THE 1949 YEAR BOOK *of* MEDICINE

(July 1948 May 1949)

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PART I

INFECTIONS

THERAPY

Defense Mechanisms of Host in Relation to Chemotherapy of Acute Bacterial Infections are discussed by W Barry Wood Jr[1] (Washington Univ) There are two conflicting doctrines concerning nature of immunity to infectious disease Humoral immunity involving antibodies originated in the work of Pasteur and intracellular immunity is based chiefly on the work of Metchnikoff Reaction to chemotherapy occurs so quickly that it must be associated with cellular immunity rather than with development of antibodies

Most bacteria causing acute infections in man are extracellular parasites Their virulence is due at least in part to capsules which protect them from phagocytosis and to metabolic products which injure phagocytic and other cells of the host In contrast most bacteria causing chronic infection are essentially intracellular parasites which survive in cell cytoplasm Since little is known about intracellular factors of immunity in chronic disease the present discussion is limited to the extracellular environment of acute infections

Sulfonamides are bacteriostatic whereas penicillin is not only bacteriostatic but often bactericidal Even penicillin however affects only rapidly proliferating bacteria so that final elimination of organisms depends on phagocytosis Information is most complete concerning natural defenses of the lungs It has been shown that virulent pneumococci Friedlander s bacillus beta hemolytic streptococci and staphylococci are susceptible to surface phagocytosis in which leukocytes trap organisms

(1) C 1 J M d 30 65 69 F b ry 1949

PUBLISHER'S NOTE

The dates appearing under the title of this YEAR BOOK indicate that journals received within that period have been reviewed by the editors in selecting the articles abstracted herein.

The symbol ® in this YEAR BOOK indicates that a drug is a proprietary.

PART I

INFECTIONS

THERAPY

Defense Mechanisms of Host in Relation to Chemotherapy of Acute Bacterial Infections are discussed by W Barry Wood Jr[1] (Washington Univ) There are two conflicting doctrines concerning nature of immunity to infectious disease Humoral immunity involving antibodies originated in the work of Pasteur and intracellular immunity is based chiefly on the work of Metchnikoff Reaction to chemotherapy occurs so quickly that it must be associated with cellular immunity rather than with development of antibodies

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(1) Cinc nat J Med 30 65 69 Feb y 1949

against alveolar walls or against other phagocytes before ingesting them. There is little information on surface phagocytosis in tissues other than the lung, but the rapidity with which phagocytosis is carried out here precludes the possibility that it depends on the presence of antibodies.

Inflammatory reaction in lymph nodes is surprisingly rapid. In one to three hours after injection of organisms into the footpad many polymorphonuclear leukocytes migrate into regional lymph node sinuses from the capillaries of the node and form a veritable log jam. Bacterial phagocytosis must then take place.

Experiments in Wood's laboratory indicate that penicillin even in high concentrations fails to kill pneumococci when organisms have ceased to multiply. This phenomenon must account for failure of penicillin to affect certain infections such as empyema or meningitis. Walling off of infection further prevents access of penicillin to organisms.

Antibodies cause agglutination and consequent immobilization of pneumococci and facilitate phagocytosis, but these substances are not present until late in the course of infection. Although antibodies undoubtedly play a role in recovery in untreated and in relatively late bacterial infections, they are unimportant in chemotherapy as compared with prompt and efficient mechanisms of cellular defense.

Effect in Patients of Streptococcic Fibrinolysin (Streptokinase) and Streptococcic Desoxyribonuclease on Fibrinous, Purulent and Sanguineous Pleural Exudations. William S. Tillett and Sol Sherry[2] (New York Univ.) injected preparations derived from broth cultures of hemolytic streptococci into pleural cavities of patients with various types of pleural exudation. It was hoped that the fibrinolytic substances elaborated by streptococci would cause lysis of solid elements in pleural exudate.

(2) J. Clin. I[illegible] 28:1[illegible]3 [illegible]190, Ja[illegible] 1949

Purified concentrates containing streptococcic fibrinolysins (streptokinase) and desoxyribonuclease were injected into pleural cavities of 23 patients Intrapleural fibrinolytic and proteolytic changes attributable to activity of streptococcic fibrinolysins were demonstrable in samples of exudate taken at repeated intervals after each injection Figure 1 shows two specimens of pleural exudate from a patient with pyopneumothorax The specimen at the left taken before injection shows an exudate 70 per cent of which is sediment with a viscosity 150 times that of water By contrast the specimen at the right removed from the chest an hour after injection of streptococcic concentrate contains only 23 per cent sediment and has a viscosity only four times that of water



Fig 1—R p d ly by t ptoc co t at f p l t d t f m pl al a y f p t t th py p m th (C t y f 3 ll tt W S t Sh y S J Cl f r t g t 8 273 190 J 1949)

Toxic manifestations were limited to transitory fever leukocytosis and malaise Permanent alterations of pleural fluid viscosity were not expected and were not found

Desirability of preventing fibrin formation or of causing liquefaction of fibrin already present depends on factors which must be evaluated in each patient Fibrin formation in acute infection restrains dissemination of infection but may prevent introduction of antibiotic and other antibacterial substances Eventual formation of scar tissue or adhesions may be undesirable

[This is a new and *promising idea* use of the fibrinolysin of the streptococcus to *destroy fibrin in empyema* cavities *and in* hemothorax Evidence of real liquefying effect is shown in the illustration In addition to empyema and hemothorax one wonders about possible application *of this agent* to treatment of certain types of *granulomatous infection* bacterial endocarditis *etc Further* observations will be eagerly awaited —Ed]

Occurrence of Superinfections during Antibiotic Therapy is reported by Emanuel Appelbaum and William A Leff[3] (New York Univ)

CASE 1 —Man 45 was given sulfadiazine and then penicillin for pneumococcic pneumonia He improved temporarily then became very ill *Bacillus coli* was found in sputum and blood Streptomycin was administered with recovery

CASE 2 —Man 44 was treated with sulfadiazine and then penicillin for pneumococcic pneumonia On the eleventh hospital day gram positive cocci in sputum culture were overgrown by gram negative bacilli and the clinical condition was worse After streptomycin therapy he recovered

Tendency of penicillin resistant organisms chiefly B coli and other gram negative bacilli to thrive in patients given penicillin has been recognized previously To prevent this occurrence it has been suggested that penicillin and streptomycin be given together The authors do not consider routine use of combined therapy warranted because incidence of such new infections is not high In addition such indiscriminate use of both drugs may sensitize certain patients to their later use They recommend careful watch for new infections and use of each antibiotic in a specific manner to be determined by bacteriologic study Bacteriologic examinations should be made frequently and carefully in all patients before and during treatment with antibiotics to detect presence of superinfections

Bacteriologic Studies on Aureomycin conducted by Thomas Fite Paine Jr Harvey Shields Collins and Maxwell Finland[4] (Harvard Univ) indicate that this substance has considerable antibacterial action in vitro against many gram positive and gram negative bacteria

(3) J A M A 138 119 121 S pt 11 1948
(4) J Bact 56 489 497 Oct be 1948

Data on sensitivity to aureomycin of 186 strains of organisms isolated from patients at Boston City Hospital are presented in the table Of the organisms tested only Proteus vulgaris and Pseudomonas aeruginosa were consistently resistant to aureomycin

Weight for weight aureomycin was less effective than streptomycin for most cocci It was about as effective

DATA ON AUREOMYCIN SENSITIVITY OF RECENTLY ISOLATED BACTERIA

Or n sm	N Strains Te	I H Co cent * M cr gram/M (Com et)
Aerobacter aerogenes	10	12 5 50
Diplococcus pneumoniae	13	0 1 1 0
Escherichia coli	31	3 1 100†
Hemophilus hemolyticus	1	0 8
Hemophilus influenzae type ?	5	1 0-2 0
Hemophilus influenzae type B	1	~0
Klebsiella pneumoniae	4	6 3 0
Neisseria catarrhalis	2	~0
Neisseria gonorrhoeae	37	0 25 1 0
Neisseria meningitidis	1	0 5
Pleuropneumonia like	1	0 75
Proteus morgani	1	4 0
Proteus vulgaris	13	175 250
Pseudomonas aeruginosa	7	100 250
Salmonella sp	6	3 1 75
Salmonella typhosa	6	3 1 ~5
Staphylococcus albus	?	1 0-2
Staphylococcus aureus	27	1 0 12 5‡
Streptococcus faecalis	2	6 3
Streptococcus mitis	4	0 8 6 3
Streptococcus pyogenes	12	0 5 1 0

* Som f th se t st w m d by tube d l ti m thod d th by a f ce t ak method
† Tw ty tw tra b b ted by 1 5 25 m g m /ml
‡ Tw nty fou f these nhib ted by 1 2 m ogr m /ml

as streptomycin against most gram negative bacilli and was equally effective against penicillin sensitive and resistant staphylococci as well as streptomycin sensitive resistant and dependent organisms

In dry form aureomycin is stable for six months In distilled water it may be stored without deterioration for two or three weeks in the refrigerator or incubator

[This is a new and promising idea use of the fibrinolysin of the streptococcus to destroy fibrin in empyema cavities and in hemothorax Evidence of real liquefying effect is shown in the illustration. In addition to empyema and hemothorax, one wonders about possible application of this agent to treatment of certain types of granulomatous infection bacterial endocarditis, etc. Further observations will be eagerly awaited.—Ed]

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(3) J A M A 138 119 121 Sept 11 1948
(4) J Bact. 5 489-497 October 1948.

monia Q fever lymphogranuloma inguinale granuloma inguinale Rocky Mountain spotted fever and brucellosis as well as many infections caused by gram positive and negative organisms

Chloromycetin* is effective against rickettsial disease typhoid and typhus and will probably be found valuable against viruses and gram negative organisms

Not only is polymyxin more active than streptomycin against streptomycin sensitive gram negative organisms but also against many streptomycin resistant gram negative organisms Polymyxin is decidedly active against Hemophilus pertussis Hemophilus influenzae Escherichia coli Aerobacter aerogenes and Pseudomonas aeruginosa and the authors do not hesitate to use polymyxin when danger of the disease outweighs danger of renal damage from the drug From 3 to 6 mg /kg body weight is given daily buffered to pH 7 4 and given at four hour intervals Polymyxin causes renal dysfunction varying from fixation of urinary specific gravity to oliguria and azotemia

Aureomycin deteriorates rapidly in solution Although dosage has not been definitely established it is recommended that severely ill patients be given 60 mg /kg daily The first three doses each containing one sixth of the total daily dose are given at hourly intervals for 3 hours and thereafter one sixth of the total daily dose is given every 4 hours until temperature has been normal for 24 hours Daily dose is then halved and administration is continued every six hours until infection is eliminated In less severely ill patients dose may be 30 mg /kg daily from the start The drug is given orally There is little tendency of bacteria to develop resistance

No significant ill effects result from use of aureomycin or chloromycetin * Nausea from aureomycin is partially prevented by simultaneous administration of aluminum hydroxide Stools may become bulky from alteration of bacterial flora of the bowel

[Giving dosage schedules by the mg /kg body weight scheme

at 37 C In contrast to streptomycin which acts most efficiently in alkaline mediums aureomycin acts most efficiently in acid mediums

No aureomycin inhibiting substances similar to penicillinase could be found Most bacteria studied showed little tendency to become resistant to aureomycin Clinical observations seem to verify this absence of acquired aureomycin resistance among most organisms

[Aureomycin has already had extensive clinical trial and many reports will be found in this YEAR BOOK It appears to have wide usefulness against pathogenic micro-organism including both gram positive and gram negative bacteria rickettsia and even some viruses (lymphogranuloma venereum atypical pneumonia) A recent report also indicates that it is effective in amebiasis Note in the table that it is comparatively active against Staphylococcus aureus This may be of special importance in view of the apparent increased incidence of penicillin resistant staphylococci (see this YEAR BOOK pp 23 and 24) —Ed]

Experimental and Clinical Use of Polymyxin, Chloromycetin* and Aureomycin Studies by Perrin H Long Emanuel B Schoenbach Eleanor A Bliss Morton S Bryer and Caroline A Chandler (Johns Hopkins Univ) indicate that penicillin remains the drug of choice for gram positive organisms Polymyxin is by far the most effective drug known for gram negative bacilli but its toxicity is so great that its use is usually reserved for organisms which fail to respond to streptomycin Chloromycetin* and aureomycin are at present used chiefly against organisms not previously influenced by antibiotics i e viruses and rickettsia In addition chloromycetin* is effective against typhoid and aureomycin against brucellosis Effect of these agents on acid fast bacilli and spirochetes remains to be determined

The only exception to the rule that penicillin is the drug of choice for gram positive organisms is in Lancefield s group D streptococci which respond best to aureomycin The only gram negative organism not affected markedly by polymyxin is proteus

Aureomycin is of value in treatment of virus pneu

(5) California M d. 70 157 166 March 1949

could not be done regularly but no patient was dis charged until he had three *negative stool cultures* *In* two patients stool cultures were positive after comple tion of the chloromycetin® course but later became nega *tive Urine cultures were consistently negative before* during and after therapy

In two patients relapses occurred 10 and 16 days after *fever had subsided Recurrent infection responded*

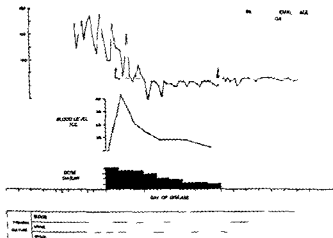


Fig 2—R p n to bl my et ® the pr ca f typh d f (Cou t sy f W odwa d T E t I A I c Med 29 131 134 J ly 1948)

promptly to chloromycetin® in both The only other com plications were hemorrhage in one patient and perfora tion in another

Figure 2 correlates the rapid fall in temperatures with rise in blood concentration of chloromycetin® in one pa tient Blood and urine cultures are shown to be con sistently negative after institution of treatment and stool cultures negative with two exceptions

(Here is the first really effective therapy for typho d fever The good results reported have already been confirmed by other work

seems unnecessarily complicated It makes dosages difficult to re member and is not particularly logical since the principal host factors are rapidity of renal elimination and inactivation of the drug These do not vary markedly with body weight In general the do es of both aureomycin and chloromycetin® range from 1 to 6 Gm daily

It is most unfortunate that polymyxin may cause renal damage as it would otherwi e have great clinical value For serious gram negative infections especially if Ps pyocyaneu is involved use of polymyxin is justified and may be life saving We recently observed a case of pyocyaneus meningitis cured with polymyxin after sulfonamides and aureomycin had been given without effect—Ed]

Preliminary Report on Beneficial Effect of Chloro mycetin® in Treatment of Typhoid Fever During an in vestigation of the chemotherapeutic value of chloromy cetin® in treatment of scrub typhus fever on the Malayan peninsula Theodore E Woodward Joseph E Smadel Herbert L Ley Jr Richard Green and D S Mankikar[6] took the opportunity to use the drug on 10 patients with typhoid fever

Diagnosis in each patient was confirmed by blood cul ture before treatment which was started during the sec ond week of disease An initial dose of 50 mg /kg orally was followed by 0 25 Gm every two hours until tempera ture was normal and then 0 25 Gm every three or four hours for five days For the first 24 hours blood concen trations of chloromycetin® were 40 80 gamma/cc (160 320 times the concentration necessary to inhibit Eber thella typhosa in culture) For the next three days the concentration was 20 gamma/cc

Evidence of improved general condition was usually apparent within 24 hours after start of specific treat ment Mean duration of fever after beginning chloromy cetin® treatment was 3½ days in these patients In 8 of the 10 blood cultures were taken daily for five days after initiation of treatment All blood cultures remained ster ile In two patients blood cultures were taken two four and eight hours after initial dose of chloromycetin® These blood cultures also remained sterile Stool cultures

(6) Ann Int Med 29 131 134 July 1948

could not be done regularly but no patient was discharged until he had three negative stool cultures In two patients stool cultures were positive after completion of the chloromycetin* course but later became negative Urine cultures were consistently negative before during and after therapy

In two patients relapses occurred 10 and 16 days after fever had subsided Recurrent infection responded

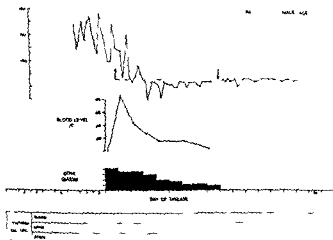


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[Here is the first really effective therapy for typhoid fever The good results reported have already been confirmed by other work

ers Treatment should perhaps be continued two to three weeks to avoid relapse In this disease chloromycetin® is definitely superior to aureomycin One would expect chloromycetin® to be similarly effective in other salmonella infections but little information is available to date — Ed]

Aureomycin in Typhus and Brucellosis In the summer of 1948 during an investigation of antimicrobial therapy of typhoid fever with various drugs 11 patients with typhus and 5 with brucellosis were given aureomycin As striking improvement occurred *uniformly* in typhus and brucella infections Vernon Knight Francisco Ruiz Sanchez Amado Ruiz Sanchez and Walsh McDermott[7] (New York City) report observations on these cases

Institution of therapy was followed by remarkable im*provement in all signs* and symptoms of typhus Change was clearly evident in the first 24 hours in all patients although in four the fever persisted longer (in one for *72 hours*) Headache and gastrointestinal symptoms disappeared overnight and rash when present at start of therapy faded completely in two to three days Other than *occasional* vomiting of the medication no significant toxic effects were observed In no instance was vomiting severe enough to cause therapy to be discontinued There *were no relapses during three to six months* follow up

Most patients were given 6 Gm aureomycin the first day in divided doses and 4 Gm daily thereafter for an *additional five days*

Results of aureomycin therapy in febrile patients with brucellosis were striking Temperatures which had reached a daily high of 101 3 F or more *before* treatment promptly fell and were within normal range within four days Improvement in other clinical manifestations was also rapid with loss of joint pains and malaise and return of appetite and general well being within a few days The most impressive evidence of antimicrobial effect was the course of infection in a patient with acute meningoencephalitis *whose spinal fluid revealed 55 mono*nuclear cells/cu mm Defervescence started soon after

(7) *Am J Med 6 407 416 Apr l 1949*

first administration of aureomycin and after 72 hours the patient was completely afebrile Moreover disappearance of fever was accompanied by marked diminution of evidences of central nervous system involvement The patient was discharged on the fourth day of treatment and remained asymptomatic in the four months which followed

Since this material was submitted for publication eight more patients with typhus fever have been successfully treated with aureomycin One patient given 25 mg/kg daily for 36 hours showed appreciably less response than those receiving larger doses From present observations it appears that the lowest fully effective dose may be somewhere between 50 and 100 mg/kg daily for a short period of therapy

[For confirmatory results in treatment of brucellosis see this YEAR BOOK pp 56 ff Apparently both aureomycin and chloromycetin[a] are dramatically effective in typhus fever —Ed]

Effect of Urea on Bactericidal Action of Sulfonamide Drugs Report of Five Cases of Bacterial Meningitis is made by A A La Londe and W James Gardner[8] (Cleveland Clinic) Several years ago it was reported that the inhibitory effect of sulfadiazine on growth of Escherichia coli is significantly increased by presence of urea even when a sulfonamide inhibitor such as methionine or para aminobenzoic acid is present The beneficial effect of urea was attributed to its inhibition of sulfonamide inhibitors and to enhancement of bacteriostatic action of sulfonamides Since development of sulfonamide resistance by bacteria has become significant any agent which overcomes this resistance will play an increasingly important role Urea is known to render sulfonamides more soluble and to have a solvent action on pus debris and necrotic tissue which act as sulfonamide inhibitors In addition it is relatively nontoxic mildly bacteriostatic diuretic simple to administer and inexpensive

A report of Case 1 follows

(8) J A M A 138 406 408 Oct 9 1948

Man 43 contracted meningitis due to Alcaligenes faecalis after breaking down of an operative wound following removal of a large sacral meningocele For three months large doses of sulfadiazine orally and penicillin intramuscularly and intrathecally were given in an attempt to prevent spread of the localized meningitis at the operative site Despite this therapy A faecalis was grown from spinal fluid at the end of this period and the patient s condition grew steadily worse Streptomycin intrathecally temporarily sterilized the spinal fluid but had to be discontinued because injection caused severe pain Urea 30 Gm every four hours was then started with 2 Gm sulfadiazine every four hours and 30 000 units of penicillin every three hours Temperature returned to normal in 24 hours and spinal fluid culture was negative in 4 days The patient was discharged after 15 days of this therapy and remained well Blood urea during therapy ranged from 24 to 180 mg /100 cc The only symptoms attributed to elevated blood urea were somnolence and loss of appetite

Similar results were achieved in a case of meningitis due to Klebsiella pneumoniae which developed while the patient was receiving prophylactic doses of penicillin two cases of meningitis due to Esch coli and a case of meningitis probably due to Staphylococcus albus

Since this form of therapy is simple safe and effective the authors suggest that it be tried in sulfonamide resistant infections before resort to streptomycin

[The potentiating effect of urea on the antibacterial effect of the sulfonamid s is well established This form of therapy is worth keeping in mind when dealing with stubborn gram negative bacillary infections such as those described —Ed]

Toxic Reactions during Streptomycin Sulfadiazine Therapy of Brucellosis Published opinions indicate that toxicity of streptomycin to the central nervous system is confined almost entirely to the eighth cranial nerve predominantly to its vestibular branch A few isolated instances of more generalized brain involvement have been reported In patients with meningitis receiving streptomycin intrathecally it is uncertain whether symptoms result from disease or treatment Norman B McCullough and C Wesley Eisele[9] (Univ of Chicago) report three cases in which toxic reactions of the central

(9) J A M A 139 80 82 Jan 8 1949

nervous system seemed out of proportion to the small doses of streptomycin and to involve more widespread areas of the brain than has generally been recognized

CASE 1—In a woman 24 initial illness was accompanied by intense headache and stupor During the next two years she had at least 10 episodes of fever and continued to have headache mental sluggishness and poor memory A course of streptomycin and sulfadiazine was instituted but the second day she experienced severe headache semistupor mild disorientation bilateral ptosis of eyelids eye muscle weakness blurred vision paresthesias and hypalgesia of the face tremulousness of lips tinnitus and paresthesias of extremities Spinal fluid was normal Because of the possibility that these symptoms resulted from streptomycin toxicity daily dose was reduced from 4 to 2 Gm During the eight days this reduced dose was given symptoms and signs subsided somewhat

Streptomycin was discontinued for a week and when administration was resumed symptoms reappeared

CASE 2—Woman 50 had contracted brucellosis 10 years before After the acute illness she had persistent headache insomnia and radicular pains and recurrent fever Combined streptomycin and sulfadiazine was started The second day severe generalized headache dizziness blurred vision diplopia ptosis of eyelids inability to move the eyes upward and some nuchal rigidity developed These appeared after 2 Gm streptomycin had been administered and became maximal after 4 Gm They persisted but did not progress during the rest of the course of streptomycin and thereafter disappeared Spinal fluid was normal

CASE 3—Woman 49 with an unconfirmed diagnosis of brucellosis was given streptomycin sulfadiazine at her own urgent request The fourth day of therapy urinary retention developed Seven months later urinary retention was still present and was attributed to neurogenic bladder dysfunction which could not be related to any other neurologic disease

The authors have found circumoral paresthesia and objective hypalgesia common in patients given both streptomycin and sulfadiazine It is suggested that the two drugs together are more toxic than either alone and that the reaction elicited may be Herxheimer in type It is impossible to determine of course if these reactions result primarily from disease or from treatment

[This report of severe toxicity resulting from combined sulfonamide and streptomycin therapy is noteworthy because there is a

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Since this form of therapy is simple safe and effective the authors suggest that it be tried in sulfonamide resistant infections before resort to streptomycin

[The potentiating effect of urea on the antibacterial effect of the sulfonamides is well established This form of therapy is worth keeping in mind when d aling with stubborn gram negative bacillary infections such as those d scribed —Ed]

Toxic Reactions during Streptomycin Sulfadiazine Therapy of Brucellosis Published opinions indicate that toxicity of streptomycin to the central nervous system is confined almost entirely to the eighth cranial nerve predominantly to its vestibular branch A few isolated instances of more generalized brain involvement have been reported In patients with meningitis receiving streptomycin intrathecally it is uncertain whether symptoms result from disease or treatment Norman B McCullough and C Wesley Eisele[9] (Univ of Chicago) report three cases in which toxic reactions of the central

(9) J A M A 139 80 82 Ja 8 1949

cause of the hopeless outlook without streptomycin all patients continued to receive the antibiotic after hearing impairment was obvious Hearing improved in all three when therapy was discontinued One patient had severe labyrinthine disturbance with complete loss of vestibular function in addition to hearing impairment

The authors conclude that streptomycin in combination with sulfadiazine or sulfamerazine appears to be the therapy of choice in primary I s pyocyanea meningitis

[Risk of drug toxicity described in the preceding article must of course be taken in cases such as these —Ed]

Infection by Penicillin Resistant Staphylococci Mary Barber and Mary Kozwakowska Dowzenko analyzed specimens of pus from 100 patients with staphylococcic infection in one hospital between *April and June 1948* Penicillin resistant strains of Staph pyogenes were isolated from 59 patients From 39 all colonies tested were resistant and from 20 both resistant and sensitive strains were isolated Similar studies in the same hospital in *1946 and 1947* yielded *14 1 and 38 per cent penicillin* resistant strains respectively

All 59 penicillin resistant strains of Staph pyogenes produced penicillinase and when tested by streaking a single colony across a penicillin ditch plate were resistant *to at least 10 units of penicillin/ml*

Widespread use of penicillin is generally agreed to be the cause of rapid increase of penicillin resistant staphylococci There are two ways in which penicillin may have this effect Either a strain may acquire resistance to penicillin or naturally resistant organisms originally few may survive while penicillin sensitive organisms are destroyed and thus by a simple process of selection become increasingly common Evidence in support of the latter hypothesis was obtained by phage typing of penicillin resistant strains of staphylococci isolated from nine patients with operative wounds and one patient with an infected burn Eight of the 10 patients were infected

( ) La t 641 644 O t 23 1948

tendency these days to shoot the works in treating infections — Ed]

Meningitis Due to Pseudomonas Pyocyanea Report of Three Cases Treated Successfully with Streptomycin and Sulfadiazine is made by Louis Weinstein and Thomas S Perrin[1] (Boston) All three cases followed instillation of a spinal anesthetic in the same hospital during 13 days Careful check of sterilization procedures revealed no error which might have allowed contamination of instruments Skin cultures did not reveal the causative bacteria There is a good possibility that Ps pyocyanea was present in materials introduced intrathecally since this organism frequently contaminates solutions of procaine etc

Response to combined streptomycin and sulfonamide therapy was rapid in each case Streptomycin dosage ranged from 1 8 to 8 1 Gm intrathecally and from 36 5 to 227 Gm intramuscularly Because of the protracted course in the first case it was possible to assess crudely the relative merits of streptomycin and sulfonamide alone and in combination When streptomycin was given intrathecally and intramuscularly alone or with a sulfonamide symptoms tended to abate temperature dropped spinal fluid became sterile within 48 hours and number of white cells in the spinal fluid decreased Penicillin intrathecally was ineffective on brief trial A sulfonamide alone failed to control meningeal infection although large doses temporarily ameliorated severity of the disease Use of streptomycin is therefore indispensable to successful therapy of primary meningitis due to Ps pyocyanea However caution must be exercised in considering a patient cured since two patients had relapses after therapy was stopped—one patient after 32 days No essential change in sensitivity of the pyocyanea organism to streptomycin was observed during the disease

All patients had severe deafness during therapy Be

(1) Ann Int M d 9 103 117 J ly 1948

were carriers of resistant strains These figures are disturbingly high although perhaps not unexpected in view of the apparently increasing incidence of penicillin resistant strains in human infections

PNEUMOCOCCIC INFECTION

Pneumococcic Pneumonia Treated with Aqueous Penicillin at 12 Hour Intervals An investigation is reported by Philip A Tumulty and Gordon Zubrod[4] (Johns Hopkins Univ) Though efficacy *of penicillin in treatment* of pneumococcic pneumonia is well established mode of administration has been determined on somewhat empiric grounds Because it has been assumed that a blood concentration of penicillin greater than the organism s penicillin sensitivity should be maintained frequent administration of penicillin has been the practice It has not been demonstrated experimentally or clinically that this is necessary or desirable To test the efficacy of infrequent *administration of penicillin* pneumococcic lobar pneumonia was chosen because of its relatively sharp clinical end point Almost all patients admitted to the public wards of the Johns Hopkins Hospital from October 1947 to May 1948 with clearcut pneumococcic lobar pneumonia were given 300 000 units of an aqueous solution of potassium salt of crystalline penicillin G intramuscularly every 12 hours

Results in 82 patients were compared with those achieved by administering 300 000 units of penicillin in oil and beeswax every 24 hours to 58 patients in 1946 and 1947 and by administering aqueous penicillin to 69 patients in doses of 20 000 80 000 units every three hours during 1945 and 1946 In the current experiment initial 300 000 *unit dose was repeated at 12 hour intervals until* temperature had remained normal 48 hours Thereafter 300 000 units was given at 24 hour intervals for an ad

(4) New England J Med 239 1033 1036 Dec 30 1948

by staphylococci of the same phage type The authors believe a process of selection is therefore the major factor responsible for increase in penicillin resistant strains of organisms

[The increase in penicillin resistant strains encountered in one hospital in a three year period appears to be significant and reminds one of the similar rapid increase in sulfonamide resistant gonococci a few years ago Fortunately aureomycin promises to be a potent second line of defense in treatment of staphylococcic infections —Ed]

Carriage of Penicillin Resistant Staphylococcus Pyogenes in Healthy Adults Many reports in recent years indicate that there may be an increase in resistance to penicillin among strains of Staph pyogenes isolated at different times from human infections during penicillin treatment Many workers have shown that nose and skin of normal persons are reservoirs of great importance for carriage of potentially pathogenic staphylococci

T D M Martin and J E M Whitehead[3] (St Thomas s Hosp London) conducted careful bacteriologic studies on 50 medical students and laboratory workers to determine incidence of penicillin resistant Staph pyogenes in nose and throat and on skin Half of the subjects were not in contact with material likely to be infected with this organism and none was infected clinically

TECHNIC —A dry swab was rubbed over tonsils and posterior pharyngeal wall A swab moistened with broth was passed into both anterior nares A dry swab was dipped into a pool of saliva between gum and lower lip Dry swabs were rubbed over skin of face hands chest abdomen and legs All were inoculated into lemco* broth and incubated aerobically overnight Subcultures were made from which colonies were isolated and smears made and stained by Gram s method

Among the 340 strains isolated 83 were coagulase-positive Coagulase positive strains were examined for penicillin resistance using the ditch plate method with a concentration of 10 units penicillin/ml agar in the ditch Fifteen strains were resistant Among the 50 persons 31 were carriers of coagulase positive staphylococci and 6

(3) B M J 1 173 175 Jan 29 1949

able in these patients as in patients given 25 000 units every three or four hours

Injections at 12 hour intervals permit undisturbed sleep decrease the number of needle pricks and save nursing time Aqueous penicillin is less difficult to administer and less expensive than penicillin specially prepared for slow absorption

[Others too have reported that pneumococcic pneumonia can be treated satisfactorily with soluble penicillin at 12 or even 24 hour intervals It should be pointed out however that the dose must be larger than when the drug is given at three or four hour intervals Procaine penicillin preparations seem to be the choice when there are to be long intervals between injections —Ed]

Treatment of Pneumococcic Meningitis John Kershman and Eric Peterson[8] (Montreal Neurological Inst) reviewed 12 cases of pneumococcic meningitis Headache was an invariable symptom and in some patients was excruciating Only slightly over half the patients had stiff neck and Kernig sign

Primary focus of infection was in the ear nose or throat in 11 patients and followed head injury in 5 and pneumonia in 2 more than one primary focus being present in some patients In every instance the etiologic agent was discovered at time of first lumbar puncture Spinal fluid was turbid to greenish yellow and under increased pressure It contained 2 000 20 000 cells cu mm and 250 875 mg per cent protein and in 11 of the 12 cases spinal fluid sugar content was 26 mg per cent or less X rays helped to uncover evidence of trauma pneumonia or infection of mastoid or sinuses

Treatment consisted of chemotherapy and treatment of focal infection Sulfonamides were given all patients nine received 2 Gm sulfadiazine by mouth initially and 1 Gm thereafter every four hours and four received sulfonamides parenterally Penicillin was given to all patients intramuscularly and in 9 intrathecally as well intraventricular administration was used in one instance Intramuscular dose varied from 5 000 to 100 000 units

(8) C M A J 59 5 7 511 Dec mb 1948

ditional 48 hours unless there was some indication for more prolonged therapy Two patients were given 600 000 units initially because of severe illness

Within limitations of this type of clinical study there was no superiority in response of patients receiving frequent doses of aqueous penicillin or repository penicillin over that of patients receiving aqueous penicillin G at 12 hour intervals What minor differences there were favored the last schedule During 1947 and 1948 only two patients with pneumococcic pneumonia died

As well as could be determined severity of the disease was comparable during the three periods of administration Fever lasted more than three days in only 27 per cent of patients given 12 hourly doses of aqueous penicillin whereas it lasted more than three days in 64 per cent of patients given penicillin in oil and beeswax and *in 35 per cent of patients given three hour doses* Among patients given aqueous penicillin every 12 hours only 9 per cent were in bed over two weeks in contrast to 19 and 25 per cent respectively of those given penicillin in oil and penicillin every three hours Period of hospitalization likewise was shortest in those given aqueous penicillin every 12 hours Though a smaller dose *would probably be effective there is little justification* for determining minimal effective dose in a disease with 30 per cent potential mortality

Aqueous Penicillin Therapy for Pneumococcic Pneumonia Injections at 12 Hour Intervals Excretion of penicillin in the urine long after it has disappeared from the blood suggested to Alison Howe Price[5] (Jefferson Med College) that penicillin is retained in tissue fluids for long periods and that it need not be administered at short intervals Between September 1945 and September 1947 he treated 65 patients with pneumonia by intramuscular or intravenous injections of aqueous penicillin at 12 hour intervals Initial dose was 200 000 units and subsequent doses 100 000 units Response was as favor

(5) J A M A 138 9 93 S pt 5 1948

authors with sulfonamides alone 93 per cent died whereas of 66 patients given sulfonamides and penicillin 62 per cent died Among 319 patients with pneumococcic meningitis reported in the literature in whom penicillin was the mainstay of treatment death rate was 49 2 per cent This compares favorably with an average fatality rate of 94 per cent among all patients treated with sulfonamides in the District of Columbia for four years

The accepted treatment regimen for pneumococcic meningitis entails daily intrathecal injection of 10 000 20 000 units penicillin plus 200 000 1 000 000 units daily parenterally This regimen has several disadvantages (1) local instillation of penicillin may cause arachnoiditis followed by myelitis and radiculitis (2) penicillin injected intrathecally is not always distributed throughout the subarachnoid space and (3) infection may follow lumbar puncture If none of these occur it is still a time consuming procedure for physicians and an uncomfortable one for patients

It has been reported that all patients given 20 000 000 or more units penicillin in 24 hours by continuous intravenous injection have detectable concentrations of penicillin in spinal fluid The authors therefore set out to treat patients with 1 000 000 units penicillin intramuscularly at two hour intervals This program was carried out in 21 patients There were eight deaths six within 24 hours of start of therapy Duration of therapy in patients who recovered was 6 days in one patient 7 days in three 9 days in one 10 days in one 12 days in one 13 days in three 16 days in one and 17 days in two

A death rate of 38 per cent among these patients is contrasted with a fatality rate of 62 per cent among patients given multiple intrathecal injections If patients who died within the first 24 hours of penicillin therapy are excluded the death rate among patients receiving massive systemic doses was 13 per cent and among those given multiple intrathecal injection 57 per cent Among patients who recovered those given mas

every three hours average being 30 000 units As soon as the patient s general condition permitted treatment of the *primary focus* was undertaken Mastoidectomy was performed on four patients sinus irrigation on three and paracentesis on one

Ten patients recovered completely One recovered with transverse myelitis and one man died from aspiration of mucus after mastoidectomy

The authors stress the necessity of early lumbar puncture for diagnosis If spinal fluid smear reveals gram negative organisms streptomycin therapy can be instituted The fluid in pneumococcic meningitis is usually laden with pus cells If spinal fluid cells are not predominantly polymorphonuclear influenza tuberculosis or yeast infection should be suspected

In patients suspected of having meningitis penicillin should be prepared for injection into the spinal fluid at the time of diagnostic lumbar puncture If fluid is cloudy 10 000 units of penicillin in 10 cc isotonic saline is injected into the spinal canal and 50 000 100 000 units is given intramuscularly every three hours Penicillin should be injected into the spinal fluid once or twice daily in the dose mentioned If it becomes apparent that free flow of spinal fluid cannot be obtained by the lumbar route intrathecal lavage with saline may be necessary to flush out fibrin deposits interfering with fluid flow In one patient this procedure was carried out with heparin added to the saline and a large amount of clotted material was obtained before the irrigating fluid finally returned clear When severe ventriculitis occurs penicillin should be injected into the ventricles through direct needle puncture

Treatment of Pneumococcic Meningitis with Massive Doses of Systemic Penicillin is reported by Harry F Dowling Lewis K Sweet Jay A Robinson William W Zellers and Harold I Hirsh[7] (Washington D C) Of 40 patients with pneumococcic meningitis treated by the

(7) Am J M S 217 149 156 February 1949

epidemic periods and in over 95 per cent in nonepidemic times

Among the rarer forms of infection is chronic meningococcic septicemia Diagnosis should be considered when there is intermittent pyrexia with crops of spots There are usually bouts of pyrexia every two or three days sometimes suggesting malaria recurrent crops of papules sometimes with petechial centers on trunk and extremities raised circular erythematous areas resembling erythema nodosum and occasional rheumatic symptoms such as pain or swelling of joints or pain in muscles tendons and bones Blood culture may be negative Sulfonamides are specific

In severe cases of the ordinary type the patient sometimes becomes stuporous or semicomatose as the disease progresses In contrast with this common clinical picture is a rare acute diffuse encephalitic syndrome in which deep coma and absence of response to stimuli appear early Most cases resemble the ordinary form for 24 hours after which deep coma develops Pyramidal involvement is indicated by extensor plantar reflexes and pareses There may be slight papilledema and stiffness of neck and back but otherwise muscles may be flaccid Rash may not be present In 700 patients with meningococcosis Banks found 13 with this form of disease Seven of them died Histologic study in four fatal cases showed congestion and edema in brain and spinal cord thrombosis in and hemorrhage around small blood vessels and perivascular leukocytic infiltration Purulent meningitis was present in all

Another rare form of infection is fulminating meningococcic septicemia There may be an encephalitic type in which the brunt of onslaught is on the central nervous system an adrenal type or a mixed encephalitic adrenal type The encephalitic type is of sudden onset and characterized by rapid development of lethargy stupor and deep coma with a petechial but not massively purpuric rash in 12 18 hours and normal blood pressure

sive doses of penicillin systemically had a more rapid drop in temperature Duration of pleocytosis in spinal fluid averaged 20 days in patients treated intrathecally and 8 days in those treated intramuscularly

It has not been decided whether penicillin must be present in spinal fluid to cure meningitis Presence of penicillin in high concentrations in spinal fluid however makes it likely that it is present also in adjacent nerve tissue in relatively high concentration with the intramuscular dose used

Sulfonamides have no apparent value as adjuvants in treatment of pneumococcic meningitis Among 13 patients given sulfonamides in addition to penicillin there were 7 deaths

[Here is good evidence that massive doses of penicillin given intramuscularly without intrathecal injections will produce excellent results *in pneumococcic meningitis* The only drawback is cost to the patient—about $35 a day at present rates Furthermore it should be mentioned that small doses of penicillin (10 000 units) given into the subarachnoid space do not cause troublesome local irritation —Ed]

MENINGOCOCCIC INFECTION

Meningococcosis Protean Disease H Stanley Banks[8] believes that the protean nature and broad pathology of meningococcic infection make the term cerebrospinal fever inadequate Meningococcosis is suggested as a generic name for all forms of the disease

Sequence of events in the ordinary form of meningococcic infection is generally held to be nasopharyngeal infection (usually subclinical) bacteremia and then meningitis *The exact mechanism by which the organism* passes into the blood stream from the nasopharynx is unknown Clinical histories and routine blood cultures suggest that the premeningitic bacteremia is usually short a matter of minutes or hours The ordinary type of infection is encountered in 90 per cent of cases in

(8) La t 2 635 640 Oct 23 67 681 Oct 31 1948

... the common ... complications ... arthritis and cranial nerve palsies ... cochlea are affected in labyrinthitis ... This produces a defect of balance which ... is compensated by re-education of ... mechanisms The cochlear lesion affects ... of Corti producing partial or complete nerve deafness ... ce this damage occurs early even prompt ... may not prevent it Permanent total or partial deafness in one or both ears occurs in about ... 7 per cent of cases in all age groups except 1 ... 30 in which permanent damage occurs less often Permanent deafness occurred in ... per cent of Banks's 706 patients About half of these had total bilateral deafness

Joint complications also occurred in 4.7 per cent of patients Resolution was nearly always complete in a few weeks but occasionally knee elbow and shoulder arthritis persisted for some months

Cranial nerve paralysis of the lower motor neuron type most commonly involved the sixth nerve then the seventh third and fourth in that order It is presumed due to pressure of meningeal exudate on nerves as they emerge from the brain stem Total incidence of such palsies was 5.2 per cent Cranial nerve paresis of the upper motor neuron type was seen in five patients and was more transient than the lower neuron type Less common complications of meningococcic infection include neuritis or radiculitis hemiplegia spastic paralysis convulsions thrombosis of superior longitudinal sinus various types of ophthalmia urinary retention cardiac damage glycosuria bronchopneumonia hydrocephalus and arachnoiditis

[A valuable description of the many clinical varieties of meningococcic infection by a physician who has had wide experience with the disease.—Ed.]

Fulminating Meningococcic Infections and So Called Waterhouse Friderichsen Syndrome J Howard Ferguson and Orren D Chapman[9] (Syracuse Univ) studied

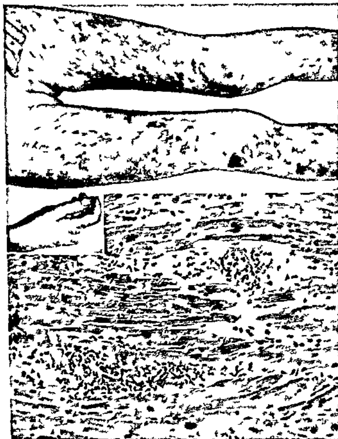
(9) Am J P th. 24 763 795 July 1948

Six of the 706 patients had this form of disease In the adrenal type (13 patients) there are fever of sudden onset and rapid appearance of generalized petechial rash which soon becomes purpuric With purpura comes peripheral circulatory failure and blood pressure is often unobtainable In contrast to the encephalitic type the mental state is clear almost to the end In the mixed encephalitic adrenal type early deep coma is combined with purpuric rash and low blood pressure (five cases) Banks objects to use of the term Waterhouse Friderichsen syndrome for cases of fulminating septicemia with massive purpura and bilateral adrenal hemorrhage because this syndrome seems to be a composite condition which includes both pure adrenal and mixed syndromes It is particularly important to distinguish between cases in which patients are comatose early and those in which they are mentally clear

There remain some fatal cases of meningococcic disease which do not quite fit into any of these categories In six patients purulent meningitis had practically subsided at time of death and could not in itself have caused death Careful histologic examination of autopsy material revealed focal vascular lesions in the brain These patients may have had an acute focal encephalitic syndrome

Mild and abortive forms of meningococcic infection occur during epidemics and may be dangerous because of slow formation of arachnoid adhesions with production of hydrocephalus subarachnoid block and sometimes compression paraplegia A chronic form may occur but is rare since introduction of sulfonamides Other rare forms of meningococcosis include primary meningococcic ophthalmia meningococcic hepatitis and meningococcic pneumonia

Not only the varieties of meningococcosis but also its complications bear witness to the protean nature of this infection Since sulfonamide therapy has reduced occurrence of hydrocephalus and the chronic form of the dis



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16 cases of fatal acute fulminating meningococcic infection In each case Neisseria meningitidis was recovered from culture of either blood or spinal fluid The clinical picture was typical of that seen during epidemics In such patients death within 12 24 hours of onset of illness is common The presenting clinical picture is frequently one of pharyngitis fever and sometimes gastrointestinal symptoms followed by rapid development of widespread petechiae cyanosis peripheral vascular collapse and death This condition has come to be known as Waterhouse Friderichsen syndrome collapse and death are attributed to massive bilateral hemorrhage into adrenal glands Though such hemorrhages occurred in some of the authors patients autopsies showed that they did not invariably occur It is suggested that collapse is the result of overwhelming bacteremia and toxemia and that adrenal hemorrhage is incidental and not in itself responsible for the clinical picture

Ten of the authors patients were males Ages varied from 3 months to 53 years seven patients being over 20 This high frequency of overwhelming meningococcemia in adults is not generally recognized Although several patients had had ordinary upper respiratory infections for two or three days 12 died within 24 hours of onset of acute illness Three survived about 30 hours and one about 60 hours

Purpura of skin (Fig 3) and mucosae was prominent in all but one patient and developed so rapidly that it could be seen to increase while the patient was under observation Increasing cyanosis delirium stupor circulatory collapse and death soon followed Lesions vary in size from punctate areas to more massive hemorrhages They were present in all but one patient

A striking observation in addition to changes in meninges and adrenals was microscopic evidence of diffuse and marked vascular damage with thrombosis in many organs Figure 4 illustrates such lesions in the myocardium Arteritis with thrombosis and striking peri

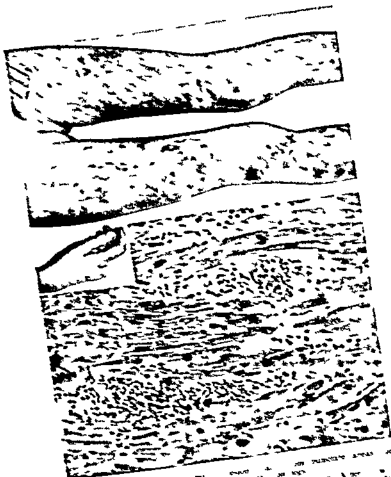


Fig. [illegible] areas [illegible]

Fig. [illegible] bottom [illegible] and [illegible] large [illegible]

Courtesy [illegible] Ferguson [illegible]

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ganisms may often be seen on direct smear and are identified by cultural and serologic characteristics At autopsy purulent meningitis with tendency to basilar distribution of exudate is observed

Course of the disease is favorably influenced by systematic treatment with sulfonamides sulfadiazine probably being the drug of choice Recovery is reported in 10 of 19 patients treated in this manner whereas only 8 of 128 treated without sulfonamides recovered Penicillin is ineffective Blood transfusion appears to be valuable Usefulness of streptomycin remains to be investigated

Prognosis further depends on age of patient and type of organism causing infection Recovery is reported in only 1 of 49 patients under age 1 month whereas 17 of 80 children in older age group lived Most patients who recovered had infections due to Salmonella paratyphi A S paratyphi B and S Panama All 45 patients with infections due to S enteritidis and its varieties died

Henderson suggests that salmonella meningitis is common enough to warrant consideration in any case of purulent meningitis

[This article was written before chloromycetin® and aureomycin came into use They deserve a trial —Ed]

TYPHOID CARRIERS

Chronic Typhoid Carrier Natural Course of Carrier State It has been generally accepted that the chronic carrier of typhoid bacilli is a permanent carrier Many authors remark on the apparent rarity of spontaneous cure of the carrier state and point out the enormously prolonged intermittency in excretion of the organisms but do not emphasize the possibility of reinfection It has never been shown whether positive cultures obtained after a long remission represent continuation of the original carrier state or reinfection A

vascular infiltration with neutrophils eosinophils and large mononuclear leukocytes were seen Although the collapse simulates that in acute adrenal cortex insufficiency absence of massive involvement of the adrenal cortex in some patients minimizes the importance of these changes in production of Waterhouse Friderichsen syndrome For these reasons the authors favor discontinuance of the term Waterhouse Friderichsen syndrome and substitution of fulminating meningococcic infection or fulminating meningococcemia

[I agree with th authors that adrenal insufficiency due to adrenal hemorrhage rarely is the dominant factor in the Waterhouse Friderichsen syndrome With modern therapy quite a few patients with this syndrome have been saved and have not shown manifestations of Addison s disease The real *essential is prompt and adequate* treatment of the meningococcic infection Adrenal cortical hormone can be given in addition and may be helpful at times — Ed]

SALMONELLA INFECTION

Salmonella Meningitis Lowell L Henderson[1] (Gorgas Hosp Ancon C Z) reports 3 cases of salmonella meningitis and reviews 144 cases from the literature The condition appears to result from a septicemia with locus minoris resistentiae an important factor A few types of salmonella account for most cases

A combination of factors peculiar to newborn infants makes them especially susceptible to this infection These include high permeability of the intestinal mucosa low resistance to bacterial infection and the trauma of birth which may weaken the meninges Clinical features of the disease in the newborn include an epidemic tendency diarrhea and a rapidly fatal course in contrast to sporadicity usual absence of diarrhea and better prognosis in older infants In both groups the course is febrile with leukocytosis Spinal fluid shows an increase in cells with early predominance of neutrophils Or

(1) Am J D s Child 75 351 375 Ma h 1948

of the original infection Reinfections or recurrences after 3 or more months of negative feces examinations occurred in 38 of the 79 patients in the 5½ years No significant difference in sex incidence of recurrences was found

Cholecystograms taken before and after the 5½ year observation period revealed no significant changes during that time There was no apparent sex difference in incidence of nonvisualization at either time

Chronic Typhoid Carrier Effect of Cholecystectomy on Bacteriologic Course A Littman J A Vaichulis and A C Ivy[3] (Univ of Illinois) performed cholecystectomy on 13 proved chronic typhoid carriers and observed them for five years after operation during which time the patients continued to live among many other typhoid carriers some of whom were heavily infected The first *stool cultures made after surgery were negative in nine* patients These were obtained 2 days to 10 weeks postoperatively In three additional patients first stool cultures were positive and the earliest persistently negative reports were not obtained until 10 weeks to 8½ months after cholecystectomy Despite massive exposure to reinfection these 12 patients remained free from typhoid organisms for the five year period

[Cholecystectomy is to date the only reasonably sure method of terminating the typhoid carrier state as attested in this and the two succeeding report However chloromycetin® effective in typhoid fever deserves a trial in typhoid carriers —Ed]

Treatment of Typhoid Carriers with Penicillin and Sulfathiazole R M Fry R E Jones B Moore M T Parker and S Thomson[4] carried out experiments on 17 typhoid carrier Treatment schedules were of three different types The first used in seven patients consisted of 1 000 000 units of penicillin intramuscularly and 1 5 Gm sulfathiazole orally every three hours for five days An eighth patient was given 500 000 units of penicillin every three hours for seven days and a total of 25 Gm

(3) J Lab & Cl M d 34 549 553 Ap 1 1949
(4) B t M J 95 96 A g 1949

Littman J A Vaichulis A C Ivy R Kaplan and W H Baer[2] attempted to clarify the bacteriologic course and role of reinfection and to ascertain any sex differences in a population of typhoid carriers maintained under one roof for many years and followed bacteriologically

The 79 chronic carriers studied were inmates of Manteno (Ill) State Hospital The original outbreak of typhoid fever at this institution was in 1939 Although the sexes lived in separate sections of the same cottage they were served from the same kitchen Moreover patients exchanged food and soft drinks and half the kitchen helpers were typhoid carriers Thus these patients not only lived in an area of endemic typhoid but were exposed more or less constantly to reinfection During 5½ years an average of 30 cultures chiefly of feces and urine were made on each patient with an average interval of 2 2 months between cultures This represents the largest mass of data obtained on a continuously observed group of typhoid carriers kept under relatively uniform conditions for so many years

In 19 patients (24 per cent) feces and urine were negative an average of 49 months range being 33-66 months Such patients may be referred to as spontaneously cured and refractory to reinfection Duration of the carrier state in these patients before spontaneous cure averaged 48 months range being 25 88 months Though 26 men were included in the study all those spontaneously cured were women Because patients with negative cultures were free from the organism for such a long period despite exposure true resistance to reinfection must have developed No explanation of the remarkable sex difference in ability to develop such resistance is known

The literature provides no proof whether recurrence of positive feces or urine in a previously known carrier after an interval of three or more months is due to reinfection or reappearance of organisms from a latent focus

(2) Am J Pub Health 38 1675 1679 December 1948

ence for several weeks after completion of treatment However organisms reappeared subsequently and hence in no instance was a carrier state actually cured Presence of calcification in the gallbladder probably contributed to difficulty of eradicating typhoid bacilli in several per sons in both groups

Though none of the carriers treated in this study was permanently cured the authors suggest that this thera peutic procedure might have some application in treat ment of the carrier state which persists occasionally after cholecystectomy or in eradicating the carrier con dition early in its development in patients convalescent from typhoid fever It is doubtful if the procedure used in these patients can be expected to cure the average chronic carrier but prolonged therapy with larger doses of the two drugs might be more fruitful

Cholecystectomy remains the only therapeutic measure of proved value for eradication of the typhoid carrier state

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DIPHTHERIA

Penicillin in Diphtheria Report of Subcommittee of Public Health Laboratory Service[6] In this investiga tion penicillin sensitivity of 284 strains of Corynebac terium diphtheriae isolated in different parts of the country was measured Most strains were tested in each of two laboratories Results showed that gravis strains of C diphtheriae are rather more resistant to penicillin than intermedius and that intermedius strains are more resistant than mitis Most of the strains tested required two or three times more penicillin for in vitro inhibition than the standard strain of staphylococcus

Of 65 patients with acute faucial diphtheria treated with penicillin in addition to antitoxin 26 of 37 receiving a three day course and 23 of 28 receiving a six day course

(6) L t 2 517 519 O t. 2 1948

sulfathiazole Typhoid bacilli were found in the stools of seven patients at the end of the course and of the eighth patient 30 days later

The second schedule consisted of four courses each lasting 2½ days during which penicillin and sulfathiazole were given every four hours Total duration of treatment was 21 days individual courses being separated by intervals of 2-4 days Total dosage was 60 000 000 units of penicillin and 90 Gm sulfathiazole Typhoid bacilli were eliminated from stools of only one of the eight patients treated in this manner

In a final attempt two carriers were given 5 000 000 units of penicillin and 1 5 Gm sulfathiazole every 3 hours for 24 hours This treatment was repeated three times with intervals of three days between courses Typhoid bacilli remained in stools of both patients

The authors concluded that despite their effectiveness against typhoid bacilli in culture penicillin and sulfathiazole are not effective in treatment of typhoid carriers

Treatment of Typhoid Carrier State Trial of Two Chemotherapeutic Procedures Robert F Korns and Ray E Trussell (New York State Dept of Health) have been unable to verify reports in the literature that the typhoid carrier state can be terminated by use of a tin compound (heptadekylaldehyde stannoxysterate) or a combination of penicillin and sulfathiazole

The tin compound was administered to 21 patients with typhoid organisms in stool None of the established carriers was cleared even temporarily of typhoid bacilli Intermittency of the carrier condition was present in 3 of the 21 patients both before and after treatment with tin

Penicillin 1 000 000 units intramuscularly every six hours and sulfathiazole 1 Gm every four hours were given for eight days to eight typhoid carriers Typhoid bacilli disappeared completely from stools for a period In two patients careful study failed to reveal their pres

(5) J L b & Clin Med. 33 1150 11 4 Septembe 1948

suspected of having acute pharyngeal diphtheria were given 60 000 units of diphtheria antitoxin and in addition 20 000 (40 000 in severe cases) units of penicillin every three hours for seven days or longer if pharyngeal mucosa was not yet entirely healed In comparison with 50 previous patients not given penicillin average length of hospitalization was cut from 57 to 45 days No deaths occurred among *penicillin treated patients* Three patients not treated with penicillin died

Penicillin 20 000 units was given every three hours for 50 doses to 44 diphtheria carriers Carrier state was eliminated in 37 Tonsillectomy was done on six of the patients who retained their carrier state and on seven previously untreated carriers Only one remained a carrier

Crawford concludes that penicillin is a valuable ad*junct in treatment of diphtheria and the diphtheria car*rier state but that it does not supplant use of antitoxin in the acute stage or obviate necessity for surgery in a selected group of carriers

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TETANUS

Tetanus Treated as Respiratory Problem is discussed by Vernon C Turner and Thomas C Galloway[8] (Evanston Ill) Recognition of the importance of respiratory obstruction due to tracheal and pharyngeal secretion in certain conditions and the ability to control it have led to a completely changed prognosis in many diseases *This is especially true of bulbar poliomyelitis* None of seven patients with bulbar poliomyelitis observed by the authors in 1947 died although five required tracheotomy One patient with myasthenia gravis accumulation of throat secretions and impending asphyxia was treated on the same basis with rapid relief

Certain other states would seem to have the same com

(8) A h S g 58 478 453 Ap 1 1949

(240 000 units daily in adults) became free from the infecting organism within four days of the end of treatment Eighty six per cent of these penicillin treated patients were bacteriologically negative 14 days after hospital admission Only 45 per cent of a previously reported series treated with antitoxin alone were bacteriologically negative within 14 days These figures support the view that penicillin treatment shortens duration of carriage of C diphtheriae in acute cases

Penicillin treatment of 31 persistent diphtheria carriers was followed by disappearance of the organism from the throat of only 13 This suggests that with penicillin therapy it may well be easier to prevent the patient with acute involvement from becoming a convalescent carrier than to cure the established carrier

Penicillin in Treatment of Diphtheria and Diphtheria Carrier State has been found by John D Crawford (Massachusetts Genl Hosp) to be highly successful Observations were made on all patients admitted for diphtheria or the diphtheria carrier state to the 279th United States Army Hospital in Berlin durin the last six months of 1946

Routine use of penicillin in diphtheria was based on results in 20 diphtheria carriers Five of them were treated with penicillin sprays every 3 hours for 10 days seven with penicillin intramuscularly in 40 000 unit doses every three hours for 25 doses and eight with 20 000 units every three hours for 50 injections The carrier state was considered terminated if at completion of treatment three consecutive cultures at 48 hour intervals and a fourth culture 1 week later were negative Penicillin sprays eliminated diphtheria bacilli in only one patient Penicillin given intramuscularly in 25 doses eliminated diphtheria bacilli in only two patients but when 50 doses were given the carrier state was eliminated in seven of eight patients

Consequently during a six month period 45 patients

(7) New England J Med 239 0 221 Aug 5 1948

was noted and it was necessary to insert an intratracheal tube and to give artificial respiration by bag for several minutes

When it was found that convulsive seizures could be controlled so readily by use of curare an attempt was made to set up a balanced system whereby the patient received a constant dose sufficient to permit relaxation of muscles and aeration but not enough to cause respiratory paralysis After 36 hours of this management it was realized that a narrow zone existed between the flaccid respiratory paralysis caused by curare and the considerable respiratory embarrassment caused by the recurrent extreme tonic muscle spasm of the trunk characteristic of tetanus In addition collection of viscid secretions in the respiratory passages added a mechanical obstacle to free exchange of gases

It was then reasoned that a tracheotomy and use of a respirator would permit maintenance of a clear air passage and positive control of air exchange With tracheotomy the thick secretion in pharynx and larynx would be by passed and the recurring laryngeal spasms would be of no consequence It would also permit direct removal of secretions from the trachea Use of a respirator would allow more latitude in dose of curare It was recognized that if a respirator were used without tracheotomy secretion would be drawn into the lower airway and the pulmonary field It seemed moreover that when the patient was fully curarized the clinical picture was similar to that seen in cases of bulbospinal paralysis in which use of the respirator proved effective after tracheotomy

With the patient on the bed of an opened respirator an oval section of cartilage was removed from the third tracheal ring (so that it would lie above the respirator collar) and a no 4 tracheotomy tube inserted When the patient s head was slid through the neck opening of the respirator collar and the respirator closed condition immediately became good Color improved pulse slowed

mon denominator of respiratory obstruction anoxia respiratory weakness and danger of drowning from aspirated secretion It occurred to the authors that tetanus with convulsions under control by curare would present much the same picture and respond to the same measures A patient with severe tetanus responded to treatment on this basis so remarkably that the authors believe it could be applied in most cases of severe tetanu with satisfactory results

In bulbar poliomyelitis if the airway is cleared and kept clear by aspiration postural drainage and when necessary tracheotomy or use of the respirator or both most patients recover Improvement may be so rapid that it indicates that the associated depression was more probably secondary to anoxia (or carbon dioxide accumulation) of peripheral respiratory origin than to infection The experience also indicated that in a patient in whom respiratory weakness paralysis or drug action makes it necessary to use a respirator it the secretion cannot be positively and constantly eliminated tracheotomy must be done first

The authors patient had severe typical clinical manifestations of tetanus As soon as diagnosis was made she was given 80 000 units of tetanus antitoxin intravenously and 20 000 units locally about the ulcer Phenobarbital was used for sedation but because spasms became increasingly severe 60 units of cu are (intocostrin®) was administered intravenously Oxygen was given by nasal catheter When curare was given the stimulus of inserting a needle set off a *tonic convulsion* during which opisthotonos became extreme and respirations ceased for a half minute at a time because of spasm of abdomen and chest Effect of the curare was dramatic opisthotonos decreased until the patient lay flat on the table jaw became relaxed as did skeletal muscles and the spasm of respiratory muscles was released so that more normal breathing was possible However when the effect of curare was at its height flaccid respiratory paralysis

prevented multiplication of Clostridium tetani or prevented further production of toxin

[Prevention of the bronchopneumonia is usually a mechanical problem The heavy sedation required to prevent convulsions depresses the cough reflex makes respiratory excursion shallow and increases the likelihood of aspiration of mucus from the throat Maintenance of a clear airway by frequent suction raising the foot of the bed and (in severest cases) by tracheotomy are all important *measures —Ed*]

ANTHRAX

Anthrax 36 Human Cases of External Type Treated Successfully with Penicillin Human anthrax is a disease for which no active prophylaxis has been developed Prevention depends largely on control of infection in animals and use of general hygienic and sanitary measures As man contracts the disease through handling of infected animals and their products it is principally an occupational disease in veterinarians and workers in wool *and leather industries*

A C LaBoccetta[1] (Philadelphia Hosp for Contagious Diseases) reports successful treatment with penicillin alone of 36 patients with uncomplicated cutaneous anthrax In 25 source of infection was traced to wool in 4 to goat skin in 3 to hides in 2 to goat hair and in 2 to horse hair The infection was commonest in wool workers who include twisters blenders carpet yarn reelers carpet burlers spinners winders sorters combers and pickers Exposed parts of the body were most frequently affected All infections were presumably contracted by direct contact with contaminated material Lesions were on the arm in 21 patients face in 10 neck in 2 and shoulder chest and back in 1 each

Discharge from the lesion was placed on a slide for examination and plain blood agar culture tubes were inoculated on hospitalization and once daily until two successive smears and cultures were negative Bacteri

(1) Am J M S 216 407 410 O t b 1948

and it seemed easier for her to rest and sleep After 10 days dosage of curare was gradually diminished and after 12 days it was discontinued Use of the respirator was stopped for increasing intervals Even after the patient could breathe well voluntarily she was much more comfortable in the respirator for several days or until she had regained strength and normal respiratory habit

Penicillin in Tetanus Clinical Analysis of 59 Cases is presented by R S Diaz Rivera Luis R Deliz and Jose Berio Suarez[9] (San Juan Puerto Rico) On admission all patients were given 100 000 units of antitetanus serum intravenously after a negative skin test for sensitivity Most of them were given 100 000 units intramuscularly also When the portal of entry was accessible it was debrided and when necessary excised after infiltration of surrounding tissues with 20 000 units of antiserum The lesion was left open and treated locally with hydrogen peroxide compresses Daily intramuscular injections of 5 000 10 000 units of antiserum were given for the next three days In accordance with the patient's needs for fluid 2 000 4 000 cc of 5 per cent dextrose in isotonic saline was given intravenously and a stomach tube was left in place Sodium phenobarbital was given hypodermically in doses of 2 gr or more every two to three hours to control convulsions Rectal instillations of ether and oil were occasionally necessary Penicillin in doses of 15 000 20 000 units was given every three hours Mortality rate was 20 3 per cent

The disease seems to have a more serious prognosis in patients over 50 or younger than 10 when the incubation period is less than five days or when the portal of entry is in the head Death resulted from respiratory paralysis and overwhelming toxemia in seven patients from bronchopneumonia in four and from extreme dehydration in one No causative agent was demonstrable in the cases of bronchopneumonia but it can be assumed to be a penicillin resistant organism It is postulated that penicillin

(9) J A M A 138 191 194 Sept 18 1948

most cases is the speed with which the first attending physician suspects the nature of the condition and summons a neurosurgeon

Spinal epidural infection is usually traceable to primary foci of inflammation located elsewhere When thi inflammation is near the epidural compartment it may invade the space by direct extension as in the case of vertebral osteomyelitis or by lymphatic spread as from a retropharyngeal abscess or mediastinal infection Osteomyelitis may in turn be traced to a more remote focus of infection Infection from distant foci is thought to reach epidural fat by the blood stream it is thus that furuncles cellulitis and pyelitis metastasize to the central nervous system Of the 20 patients 18 had acute epidural infections In 14 antecedent infections outside the epidural space were discovered these being skin infection in 7 vertebral osteomyelitis in 6 and pyelitis in 1 Skin infections were the remote primary sources of infection in two of the patients with vertebral osteomyelitis Among skin infections acne and furuncles were the most frequent

When established in the epidural space infection spreads axially along the dural surface and concentrates over the dorsum of the tube The dura is so tough that bacteria rarely penetrate it Some writers ascribe the paralysis to mechanical compression of the cord or to alterations of its blood supply Heusner believes that either may occur

The clinical events may be divided into four phases spinal ache root pain weakness of muscle sphincters and sensibilities and finally paralysis Illness begins with aching at the affected level of the spine Pain may become severe enough within 24 hours to bring the patient to the physician and at this stage fever and localized tenderness over the spine may be the only evidence of the condition Suspicion should be aroused if an extraspinal focus of chronic infection recent spinal injury or chill has occurred Usually the physician i first con

ologic confirmation of diagnosis was possible in 30 patients in most of whom both smears and cultures were positive for anthrax bacillus In the six patients for whom diagnosis was not confirmed bacteriologically characteristic appearance of the lesion left no doubt as to clinical diagnosis

Except to obtain vesicular fluid for bacteriologic study lesions were not disturbed Plain sterile dressing covered the lesion and sometimes a bland ointment was used to prevent adhesion of the dressing Because the lesion was painless it was difficult to rely on the patient voluntarily to immobilize the involved part so occasionally an extremity was splinted to discourage excessive motion Penicillin was administered intramuscularly to 33 patients (the first 3 patients were given it intravenously) most patients receiving 100 000 200 000 units in 24 hours at 3 hour intervals

Of the 30 bacteriologically positive patients 27 became negative after 72 hours of penicillin therapy In many cases lesions continued to spread and edema increased for 24 36 hours after treatment was begun indicating that penicillin apparently has no direct or immediate effect on the tissue damagin factor of cutaneous anthrax LaBoccetta concludes that penicillin intramuscularly may be safely and successfully used to treat cutaneous anthrax

[Streptomycin also seems to be effective in human anthrax —Ed]

SPINAL EPIDURAL INFECTION

Nontuberculous Spinal Epidural Infections A Price Heusner (Harvard Univ) analyzed records of 20 consecutive patients with nontuberculous spinal epidural infections at Boston City Hospital since 1930 The medical profession must be acquainted with the clinical aspects of this disorder because the decisive factor in

(2) N w E gl nd J Med 239 845 854 Dec 2 1948

CHRONIC OSTEOMYELITIS

Streptomycin in Treatment of Chronic Infections of Bone John C Wilson Jr[3] (Percy Jones Gen l Hosp) attempted to determine whether systemic and local use of streptomycin in addition to thorough sequestrectomy and meticulous wound care would hasten wound healing in patients with long standing osteomyelitis Diagnosis of osteomyelitis was always substantiated by histologic x ray and clinical evidence All patients had chronic dis charging sinuses which led to bone Purulent drainage had persisted for an average of 19 months and had usu ally necessitated bed rest Predominantly gram negative organisms were cultured from exudate of sinus tracts in all but two patients These patients had received exten sive treatment for chronic septic bone disease including repeated sequestrectomies courses of Orr treatment and millions of units of penicillin

In an effort to effect healing a plan of therapy was evolved which included thorough investigation of bac terial flora of the wound and determination of sensitivity of organisms to streptomycin and penicillin radical sequestrectomy with saucerization of the wound after adequate preparation use of penicillin and streptomycin before during and after surgery and meticulous post operative wound care

Twenty five men aged 19 39 were treated Bacterial flora was mixed in all but two cases Proteus vulgaris was the commonest gram negative organism and Staphylococcus aureus coagulase positive the com monest gram positive organism Both were present in 19 patients Intramuscular injection of streptomycin was begun 24 hours before surgery at a dosage level indi cated by organism sensitivity studies Injection was limited to 10 days because of toxic reactions with more

(3) J B & J t S g 30 A 931 944 O t b 1948

sulted the second or third day of illness when root pains are radiating from the exquisitely tender spinal segment Such symptoms are often construed as neuritis despite malaise fever tachycardia and leukocytosis (average 15 600) Correct diagnosis should be made during this phase of the condition by spinal puncture If diagnosis is not made motor weakness intervenes with gradually ascending numbness and impaired bladder and bowel control

Acute osteomyelitic syndromes differ clinically from the metastatic syndrome only in that transition from the phase of spinal ache to that of root pain is delayed days or weeks After root pain begins however the condition progresses rapidly and vertebral changes are usually demonstrable by x ray

Once diagnosis is made laminectomy for drainage of the epidural space constitutes a surgical emergency Prognosis in chronic cases is good because the syndrome develop so slowly that the patient is almost assured of operation before paralysis is complete Prognosi in acute cases has always been poor Among the patients studied all who had no paralysis at time of operation or who had paralysis less than 36 hours before operation recovered By contrast no patient whose paralysis had been present over 48 hours made a neurologic recovery and all deaths were among these patients Prognosis for life has been improved by use of antibiotics

Whether the syndrome develops slowly or rapidly spinal puncture during the phase of root pain establishes diagnosis by disclosing either epidural pus or a subarachnoid block with yellow spinal fluid containing increased protein and a few white cells but neither chemical nor bacteriologic evidence of leptomeningitis

[These infections are usually due to Staphylococcus aureus An erroneous diagnosis of poliomyelitis may be made The important thing i to perform a lumbar puncture promptly and to appreciate the urgency of the situation if a block is present —Ed]

tenderness Pain localized in the right lower quadrant and white blood cell count rose to 20 750 X ray revealed no air under the diaphragm About five hours after onset of pain the patient was operated on preoperative diagnosis being ruptured typhoid ulcer Intestines were distended but no perforation was found There was pus in the abdominal cavity and considerable pus was being discharged from a ruptured ileocecal node The abdomen was closed with a drain and penicillin streptomycin and sulfadiazine were administered for varying periods The patient was discharged well 27 days after operation

CASE 2—Girl 16 was hospitalized for abdominal pain She had had fever and malaise for two or three weeks Temperature was 104 F The abdomen was distended and tender and a fluctuant mass bulged into the left fornix Blood and urine cultures revealed paratyphoid bacilli but no typhoid organisms The hospital course was characterized by nausea vomiting and high fever Death occurred four weeks after onset of illness Autopsy revealed no intestinal perforation but one mesenteric node was necrotic and exuded pus into the abdominal cavity

Review of the literature reveals that peritonitis from suppuration of lymph nodes is extremely rare

Synergism in Experimental Infections with Nonsporulating Anaerobic Bacteria Nonsporulating anaerobic bacteria have been isolated in pure and mixed culture from human and animal infections since the early days of bacteriology Thus the role of anaerobic cocci particularly streptococci in puerperal sepsis has been established by many workers Bacterium funduliformis has been isolated from septicemias and a variety of other infections as have Bacterium melaninogenicum the fusiform bacteria and other bacteroides The nonsporulating anaerobic bacteria are notably avirulent for laboratory animals There is conversely abundant evidence of the pathogenicity of these bacteria in mixture with other organisms in pus and in culture

Previous study of bacterial flora of the normal post partum uterine cavity and the uterine cavity of patients with endometritis failed to reveal significant correlation between bacterial species present in cultures and the dis

prolonged therapy and because bacteria became drug resistant so rapidly that blood levels after 10 days are no longer bacteriostatic. Penicillin was also administered intramuscularly in doses varying from 50 000 to 100 000 units every three to four hours depending on severity and sensitivity of infection caused by gram positive organisms.

Sequestrectomy is the most important part of treatment. Unless all necrotic bone is removed no amount of antibiotic will heal the wounds. After adequate sequestrectomy wounds were not disturbed for 14 days. Dressings were then done at weekly intervals in the operating room under strict aseptic technic. Streptomycin in plasma and penicillin were applied locally at each dressing.

Results of treatment were encouraging. Healing occurred in 21 of the 25 patients. In several healing had been present for seven months and in others for two to five months at the time of writing. Patients were enthusiastic because their wounds were almost painless and odorless and dressings caused minimal discomfort. The four patients who failed to respond have had amputations.

[The title of this article is somewhat misleading. The key to cure of chronic osteomyelitis is surgical excision of all chronically infected tissue. Chemotherapy is only a helpful adjunct.—Ed.]

MIXED BACTERIAL INFECTION

Acute Peritonitis Following Rupture of Mesenteric Lymph Nodes is reported in a case of typhoid and one of paratyphoid by J. Warren Kyle and Russell H. Patterson[4] (Univ. of Tennessee).

CASE 1.—Boy 14 during the fourth week of typhoid fever had sudden onset of generalized abdominal pain and nausea without vomiting. Temperature rose from 99 to 103 F. and pulse rate from 90 to 150. Examination revealed generalized abdominal tenderness, rigidity and distention with rebound

(4) J. A. M. A. 138:816-817, Nov. 13, 1948.

activity than did the anaerobic streptococci only a few strains of which were effective

Further studies on the mechanism of synergistic activity showed that heat killed whole cultures of Bact necrophorum enhanced virulence of Str liquefaciens and that the active principle was not removed from bacterial cells by grinding with sand by digestion with trypsin or by extraction with trichloroacetic acid Heat treated but incompletely killed culture and cell suspensions of Str liquefaciens were inactive in enhancing the virulence of Bact necrophorum culture

It is concluded that synergistic activity is exhibited in infections with a variety of nonsporulating anaerobic bacteria in combination with each other or with aerobic organisms and that the property of enhancing bacterial virulence is intimately associated with the cell substance at least in the case of Bact necrophorum

[We have the impression that anaerobic streptococci are of particular importance in postpartum infections since they can sometimes be recovered in pure culture from intraperitoneal abscesses or pulmonary metastatic infections Mixed anaerobic infections are however very common and this demonstration of synergistic action by different anaerobes probably has clinical significance —Ed]

TULAREMIA

Aureomycin in Treatment of Experimental and Human Tularemia Theodore E Woodward William T Raby Williford Eppes William A Holbrook and John A Hightower[6] (Univ of Maryland) compared the effectiveness of streptomycin aureomycin and chloromycetin® in mice experimentally infected with tularemia and treated three patients with tularemia with aureomycin

Results of three separate experiments with mice revealed that aureomycin was consistently more effective than streptomycin and chloromycetin® in delaying death Chloromycetin® was least effective

(6) J A M A 139 830 832 M 26 1949

ease process Intrauterine flora was similar to that of the vagina in trichomoniasis Organisms most frequently isolated were aerobic staphylococci hemolytic and non hemolytic streptococci and diphtheroid rods and anaerobic streptococci micrococci Bacterium necrophorum and other bacteroides These results suggested an investigation of the role of bacterial synergism in production of infection by nonsporulating anaerobic bacteria The concept of the synergistic activity of two or more bacterial species in giving rise to effects not produced by the component organisms in pure culture has been demonstrated in biochemical reactions as well as in infectious processes

K Eileen Hite Marcia Locke and H Close Hesseltine (Univ of Chicago) studied experimental infections of mice with pure cultures of representative anaerobic bacteria singly and in mixture with other aerobic and anaerobic organisms White mice were inoculated subcutaneously in the abdominal wall with a constant volume of single pure cultures or mixtures thereof and size and type of the resulting lesion during its development and at autopsy after five days were observed Bacteriology of lesions was studied in direct smears and occasionally by cultures and histologic appearance of representative lesions was studied in microscopic sections of autopsy tissue Comparisons of lesions were then made on the basis of production of necrosis of the abdominal wall and by an arbitrary infectivity score

Synergism in mixed bacterial infections as seen by production of necrotizing lesions of the abdominal wall and by high infectivity scores was demonstrated using combinations of anaerobic streptococci Bact necrophorum Bact melaninogenicum other bacteroides and the fusiform bacterium with each other and with aerobic Staphylococcus albus Streptococcus liquefaciens and Streptococcus mitis The anaerobic bacteroides particularly Bact necrophorum exhibited greater synergistic

(5) J Inf t D s 84 1 9 J n Feb 1949

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Results of three separate experiments with mice revealed that aureomycin was consistently more effective than streptomycin and chloromycetin* in delaying death Chloromycetin* was least effective

* J A M A 139 830 83 Mar 26 1949

All three patients responded well to aureomycin One patient had a severe infection which would have probably terminated fatally without chemotherapy His rapid response to aureomycin with prompt recovery and that of the two other patients treated with this antibiotic suggests that aureomycin may prove as effective as streptomycin in management of this severe disease Ease of administration of aureomycin which may be given with equal effectiveness either orally or intramuscularly and its freedom from toxic complications justify a thorough clinical comparison with streptomycin in tularemia

[Further observation on aureomycin in human tularemia will be needed It is difficult to believe however that any agent will greatly excel streptomycin in this disease —Ed]

BRUCELLOSIS

Aureomycin Therapy in Human Brucellosis Due to Brucella Melitensis Because streptomycin and sulfadiazine were found effective against Brucella abortus infections this treatment was administered by Wesley W Spink Abraham I Braude M Ruiz Castaneda and Roberto Sylva Goytia[7] to patients with Brucella melitensis infections in Mexico General Hospital Mexico City When it became apparent that streptomycin and sulfadiazine were less effective in this more malignant form of brucellosis aureomycin was tried despite laboratory studies that indicated its effectiveness was less than that of streptomycin To the authors surprise aureomycin proved very effective

Temperatures became normal within two or three days after institution of treatment in 24 patients given aureomycin Improvement occurred not only in patients with acute brucellosis but also in those with chronic forms of the disease The authors recommend that a total daily

(7) J A M A. 138 1145 1148 Dec. 18 1948

dose of 4-6 Gm be administered orally for two weeks

Blood cultures taken one to three months after therapy were positive in only 3 patients Because many patients were given smaller amounts of aureomycin than those recommended it is hoped that even this small percentage of positive cultures may be eliminated

No serious side effects from aureomycin were detected Half of the patients who received 0 5 Gm aureomycin every 6 hours experienced an abrupt rise in temperature and shock 8 12 hours after institution of therapy but no serious complications followed When smaller initial doses of aureomycin were administered fewer reactions occurred The only other side effects were transient mild nausea vomiting and diarrhea

[In the 1948 YEAR BOOK OF GENERAL MEDICINE enthusiastic attention was given to treatment of brucellosis with a combination of streptomycin and sulfadiazine This form of therapy is already being supplanted by aureomycin or aureomycin plus streptomycin (see the next two articles) Also there are rumors that chloromycetin® is effective in brucellosis —Ed.]

Effect of Combined Treatment with Aureomycin and Dihydrostreptomycin on Brucella Infections in Mice was determined by Fordyce R Heilman [8] In these experiments Brucella suis organisms were injected into mice and after 48-65 hours in different experiments antibiotics were started After 10 days treatment with various antibiotics animals were killed and spleens removed After weighing spleen cultures were made by streaking the cut surface of the spleen over culture mediums or by emulsifying a piece of spleen diluting the emulsion with nutrient broth and pouring this onto agar The different therapeutic agents used included aureomycin aureomycin with dihydrostreptomycin aureomycin with dihydrostreptomycin and sulfonamides and sulfonamides with dihydrostreptomycin In a further experiment Brucella abortus organisms were used and the effect of aureomycin and dihydrostreptomycin compared with

(8) P oc. Staff M t. M y Cl 24 133 137 M 16 1949

those of chloromycetin® alone or in combination with sulfonamides aureomycin or dihydrostreptomycin

In experiments with both strains of brucella organisms aureomycin and dihydrostreptomycin were the most effective method of treatment

Combined Use of Aureomycin and Dihydrostreptomycin in Treatment of Brucellosis in man was attempted by Wallace E Herrell and Tracy E Barber[9] because of the satisfactory result of this form of therapy in animal experiments Though good results have been achieved in *human brucellosis by combined use of streptomycin and* sulfadiazine the combination is not successful in all cases and the toxicity is a disadvantage Few toxic effects from aureomycin have been reported and dihydrostreptomycin does not have as pronounced toxic effect on the eighth nerve as has streptomycin and has the same antibacterial activity

Aureomycin and dihydrostreptomycin were administered to four patients with brucellosis two from the Brucella suis strain and two from Brucella abortus strain All four recovered promptly and no recurrences followed One patient was afebrile after 48 hours treatment and two others after 72 hours

Recommended plan of treatment consists of administration of approximately 3 Gm aureomycin daily orally with simultaneous administration of 2 Gm dihydrostreptomycin a day intramuscularly Aureomycin was given in four doses at 8 a m 2 p m 8 p m and 2 a m so that sleep was interrupted only once during the night and dihydrostreptomycin was given in two or four doses daily For acute brucellosis average course of treatment is 12 14 days but in treatment of culturally proved brucellosis in which there is some localizing lesion such as involvement of the skeletal system or urinary tract or endocarditis the authors recommend that the course be extended to 21 28 days

Though it is not suggested that this treatment is spe

(9) Proc Staff M t M yo Cl 24 138 144 Ma 16 1949

cific for brucellosis the authors believe it to be the most effective method available It has the added advantages of being convenient for the patient and relatively non toxic

Impaired Cerebral Functions in Chronic Brucellosis were studied by Nathaniel S Apter Ward C Halstead C Wesley Eisele and Norman B McCullough[1] (Univ of Chicago) Attention was drawn to the psychophysical problems of chronic brucellosis by several patients with psychologic disturbances which could not be adequately explained by medical findings and appraisal of basic personality structure Ten such patients were evaluated by the combined technics of the internist neuropsychiatrist and experimental psychologist The diagnosis of brucellosis was based on convincing evidence in 8 of the 10 cases blood cultures had been positive

Evidence of organic brain disease in these patients was based chiefly on results of a battery of neuropsychologic tests designed and previously publicized by Halstead These tests are for the purpose of differentiating behavioral disturbances resulting from cortical damage and those independent of cerebral injury Validity of inferences drawn from these tests has been established by detailed study of selected neurosurgical patients with known localized brain lesions Results of these tests are expressed as impairment index A low impairment index (0-0 3) is interpreted as evidence of good biologic intelligence A high impairment index (0 5 1) in presence of normal scores on control tests is interpreted as impairment of biologic intelligence

Of the 10 patients studied impairment indexes of 0 6 or higher were found in 7 This study is interpreted as revealing severe personality changes in patients with brucellosis of a degree comparable to that seen in patients with surgical removal of the prefrontal lobes of the brain Though it is not presumed that the incidence of organic brain disease in this small series of cases is

(1) Am J P y h t 105 361 366 N mbe 1948

in any sense an indication of incidence of this complication among patients with brucellosis in general it does provide a possible explanation for the frequent diagnosis of psychoneurosis in patients with brucellosis

Brucellosis and Multiple Sclerosis Cutaneous Reactions to Brucella Antigens Because cranial nerve disturbances were found *in 5 per cent and typical multiple sclerosis was found in 0 4 per cent of a large series of brucellosis patients* E R Kyger Jr and Russell L Haden (Cleveland Clinic) attempted to determine if multiple sclerosis might be a central nervous system manifestation of chronic brucellosis Three types of skin tests for brucellosis were placed on 118 patients with multiple sclerosis Reactions were positive in 96-100 per cent but in only 21 and 31 per cent of two series of controls

To be sure that positive reactions did not result from abnormal cutaneous sensitivity to antigens in general other skin tests were used Positive reactions to OT occurred in 15 of 41 patients to histoplasmin in 5 of 34 and to coccidioidin in none of 34 tested Streptococcus vaccine produced no positive skin reactions and Hemophilus influenzae vaccine produced positive skin reactions in 10 of 19

No evidences of tularemia cholera or other diseases which cause agglutination of brucellosis antigen were found

Agglutination reactions were positive in 5 of 23 patients with multiple sclerosis Titers were 1 20 1 20 1 40 1 160 and 1 320 The last two were taken four to five weeks after skin testing Another laboratory found positive reactions in four of nine patients for whom negative agglutination tests were reported by the authors laboratory

The authors emphasize the similarity of geographic distribution and pathology of the two diseases and suggest further investigation of a possible connection

(2) Am J M S 216 689 693 December 194

[Brucellosis continues to be a complex and controversial disease It will be recalled that some years ago an attempt was made to demonstrate a relation between it and Hodgkin's disease —Ed]

HAVERHILL FEVER

Haverhill Fever (In Connection with Case Observed in Sweden) Arthur Engel[3] (Falun Sweden) reports the first case of Haverhill fever described in Sweden Mode of infection was not known In 1914 it was first reported that bites of rats and mice could infect human beings with an organism Streptobacillus moniliformis which causes an acute septic illness accompanied by skin and joint symptoms The epidemic of this disease occurring in Haverhill Mas in 1926 was spread by infected milk A subsequent epidemic in Chester Pa in 1929 involving 400 persons was also spread by infected milk

Str moniliformis is one of the most pleomorphic organisms known Its pleomorphism has led to a varying and sometimes contradictory series of reports on its nature Optimal mediums for its growth are tryptose phosphate and dextrose starch in broth or agar both with ascitic fluid or animal serum added To keep the organism alive frequent transfer is necessary The organism may escape detection because it grows poorly or not at all on ordinary agar and broth Incubation time is one to three days

Clinical picture is varied but usually is that of septicemia with a tendency to cyclic relapses Onset is usually acute with attacks of shivering vomiting and severe headache In children convulsions often occur Temperature falls to normal between the second and fifth day and during defervescence an eruption appears on extensor sides of extremities especially around the joints About a day later joint symptoms appear Re

(3) Acta med Scand 133 362 371 1949

lapses often occur at intervals of five to seven days Next to fever and vomiting headache is the most common symptom Subcutaneous abscesses and bronchopneumonia have been reported to complicate this disease

Diagnosis is established by identifying the causative organism from the blood or from the articular fluid In liquid substrates the bacteria grow in colonies or cotton balls on the surface of the sedimenting blood corpuscles

Str moniliformis is resistant to sulfonamide but sensitive to penicillin Pro nosis is invariably favorable and recovery is usually rapid except that slight joint symptoms may persist for long periods

Diagnosis in the author s case was confirmed by finding a high agglutination titer to Str moniliformis

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LEPTOSPIROSIS

Four Cases of Leptospira Canicola Infection in England are presented by I J M Laurent T St M Norris J M Starks J C Broom and J M Alston[4] in a symposium Though only about 100 cases of human canicola fever have been reported the disease has been found in most parts of the world

CASE 1—Youth 19 was hospitalized because of a four day illness characterized by headache fever and a rash on the face and chest diagnosed as meningitis The neck was stiff but Kernig s sign was not present and spinal fluid was normal Temperature was 100 8 F and there was marked conjunctivitis On the third hospital day Kernig s sign was present and there were 290 cells/cu mm spinal fluid The next day rash fever and meningitic signs subsided Diagnosis of canicola fever was finally established by agglutination tests Fifty days after onset the serum agglutinated L canicola in a titer up to 1 3 000 about 100 days after onset the titer was 1 300

CASE 2—Woman 28 had a history similar to that of the first patient On admission spinal fluid contained 1 320 cells/cu mm The thirtieth day after onset agglutination was positive with L canicola in a titer of 1 3 000

(4) Lancet 2 48 51 July 10 1948

CASE 3—Woman 40 had a history similar to that of the two previous patients with in addition vomiting and blurring of vision The skin rash resembled erythema nodosum The neck was stiff but Kernig s and Brudzinski s signs were not present. Spinal fluid on admission contained 48 cells/cu mm but two days later contained 233 cells She was apparently well 2 weeks after onset but a week later had a relapse which lasted 10 days Serum agglutinated L canicola to a titer of 1 3000 on the twelfth day of illness

CASE 4—Youth 18 was hospitalized because of listlessness vomiting abdominal pain and headache of four days duration There were slight right sided ciliary injection neck rigidity and Kernig s sign Lumbar puncture revealed 380 cells/cu mm all lymphocytes On the seventh day of illness a strong positive agglutination with L canicola was obtained

Of the four patients three had dogs when their illnesses began Previous studies have shown that 30-40 per cent of dogs harbor L canicola in stools

Human canicola infection is not always accompanied by meningitis At onset all four patients had headache and fever with vertigo vomiting or abdominal pain Eye signs—conjunctival or ciliary injection photophobia pupil inequality misty vision or blurred disk edges—developed in all patients during the illness Relative prominence of such eye signs has been noted in meningeal forms of Weil s disease Stiff neck was present in all four patients and Kernig s sign in three One patient had weakness of dorsiflexors of the foot Maximal abnormal findings in spinal fluid varied from 233 to 1 320 cells/cu mm (almost all lymphocytes) and 20 400 mg per cent protein In three patients leukocyte counts showed little abnormality except for relative lymphocytosis Though jaundice is often thought to be an essential feature it may not be present The authors suggest that leptospiral infection be considered in differential diagnosis of all cases of lymphocytic meningitis

[Although pleocytosis is recognized as a common occurrence in Weil s disease it is becoming increasingly evident that a clinical picture of meningitis without any evidence of hepatitis or nephritis may be the presenting complaint in leptospiral infection especially with strains other than icterohemorrhagica —Ed]

Generalized Nonfatal Histoplasmosis in an Infant Though it had been suggested that histoplasmosis is responsible for pulmonary calcifications found in certain persons with negative tuberculin tests not until 1948 was a report made on patients with this disease studied during the acute phase who subsequently recovered Another such case is added by Richard W Blumberg Isaac Ruchman and Ralph J Johansmann[5] (Univ of Cincinnati)

Girl aged 2 months had had nasal discharge and cough for two days She appeared well developed and well nourished and irritable but not acutely ill *Temperature* was 99 3 F *The only* positive physical findings were a mucoid nasal discharge and firm nontender enlargement of the liver 4 fingerbreadths below the costal margin and of the spleen 2½ fingerbreadths below the costal margin There was no lymphadenopathy

During three weeks hospitalization size of liver and spleen remained essentially unchanged Red cell count remained around 3 000 000 and hemoglobin 7 8 Gm per cent Body temperature ranged from 99 to 100 F and occasionally rose to 101 F Tuberculin and histoplasmin skin tests were negative but both mother and father had strongly positive histoplasmin skin tests Histoplasma *capsulatum* was isolated *from blood culture* and from culture of material obtained by biopsy of the liver and bone marrow

After diagnosis was made the patient was transfused She ate well and gained a little weight She continued to do well after leaving the hospital and when last observed at age 16 months had continued to gain weight. Liver was 1½ fingerbreadths below the costal *margin* and *spleen* 1 *fingerbreadth* below the costal margin X ray of the chest taken one year after onset of infection showed no evidence of calcification or other abnormalities *Serum obtained after discharge from the* hospital fixed complement strongly and a histoplasmin skin test repeated three months after the first test was positive

A similar change in skin sensitivity from negative to positive after recovery from the acute phase of histoplasmosis was reported in three other patients who recovered from this disease It seems likely that during the

(5) Pediat cs 3 296 30 March 1949

acute phase the patient was in a preallergic state similar to that often seen in early tuberculous infections

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MYCOBACTERIAL INFECTION

New Mycobacterial Infection in Man is discussed by P MacCallum Jean C Tolhurst Glen Buckle and H A Sissons[6] (Melbourne) on the basis of six cases of skin ulceration with invasion by acid fast bacilli (Fig 5) and laboratory studies The ulcers were first thought to be tuberculous a diagnosis which the finding of acid fast bacilli appeared to confirm Organisms were so abundant (Fig 6) that their presence was obvious even with Gram s stain which first revealed them as diphtheroid forms in histologic sections Abundance and grouping of the bacilli and absence of the common histologic pattern of tubercle however cast doubt on this diagnosis from the beginning When material from three patients was examined bacteriologically the organisms despite their abundance in tissues and exudate failed to grow on any of the mediums commonly used for cultivation of tubercle bacillus and glandular or other lesions did not result from guinea pig inoculation This strengthened the suspicion that the organism was unusual and causally related to the ulcers

Five patients came from the same district a mixed farming one Inquiry about a possible animal reservoir gave no immediate clue to further investigation along this line The patients lived in good home conditions at widely separated points and were strangers

Attempts to cultivate the acid fast organism directly from tissues of the first four patients were unsuccessful Growth in the first case was obtained only after passage through rats but as the result of experience gained with organisms so established direct cultivation from the ulcer was successful in the sixth case

(6) J P th & B t 60 93 1 J ry 1948

The ulcers were characterized grossly by indolent extension from the center of a small breach in a solitary area of inconspicuous slightly irritable induration by intractability to treatment by pyogenic reaction and edema and often by acceleration and aggravation of the



Fig 5 (top) —Ul n f m day bef x s n (C se 6)
Fig 6 (bott m) —Sect f k n C se 4 l w pow Tw la g da k reg l m a coll ct n of c d f t b ll Z ebl N lse a d hema to yl n ed d f × 160
(Cou t y of M cC ll m I et / J Path & B ct 60 93 122 J ry 1948)

condition by the therapeutic measures used and by sloughing and denudation of large areas with little or no disturbance of health and absence of complications. The lesions spread by extension of marginal induration with breakdown resulting in steep sided or even under

cut edges of scalloped outline exposing necrotic looking tissue on floor and walls

Histologic examination of tissue excised from margins or base of ulcers showed certain features in common Tissue lining the ulcer wall and floor was necrotic necrosis being most extensive in fatty tissue in which it extended beneath the dermis for varied distances Outlines of affected fat cells were obscured so that the tissue appeared smeary Tenaciously acid fast bacilli were found in great numbers in every instance grouped characteristically in sharply defined oval or rounded masses often as great in diameter as fat cells Vascular engorgement edema and polymorphonuclear emigration around the necrotic focus varied but appeared to be correlated with the degree of pyogenic infection No sign of tubercle follicles giant cells endothelioid grouping or caseation was seen in any section

Difficulty of cultivation of the organism and its behavior toward laboratory animals raise the question of its relation to other mycobacteria especially those of leprosy and tuberculosis However no such single ulcer manifestation as a sole sign of leprosy has been recorded so far as is known so that probabilities are against these cases being leprous Whereas leprosy is not known to assume this ulcerative form there are clinical manifestations of tuberculosis which are virtually indistinguishable from those encountered in these cases However though clinical distinction from tuberculosis is not so clearcut failure to demonstrate tuberculosis by the usual laboratory procedures excludes this diagnosis also

The investigations provide valuable new means of comparative examination of the mycobacterial group A mycobacterial infection cannot be dismissed as etiologically unimportant on the ground of failure to cultivate the organism under ordinary laboratory conditions or failure of guinea pig tests Moreover presence of diphtheroid bacilli in a section of tissue should always

The ulcers were characterized grossly by indolent extension from the center of a small breach in a solitary area of inconspicuous slightly irritable induration, by intractability to treatment by pyogenic reaction and edema and often by acceleration and aggravation of the



Fig 5 (top) —Ulce n f m d y b fo e e (Case 6)
Fig 6 (bottom) —Section f k n Case 4 low pow Tw l g d k r egul m a c ll ct ons f d fa t b ll Zehl Ne l n d h m t yl d ed f m × 160
(Courtesy of MacCallum P et l J I th & B t 60 93 12 J a y 1948)

condition by the therapeutic measures used and by sloughing and denudation of large areas with little or no disturbance of health and absence of complications The lesions spread by extension of marginal induration with breakdown resulting in steep sided or even under

temperature below 37 C Though growth at best is slower and scantier than that of human tubercle bacilli no further difficulties have been encountered in culture of the organism at temperatures of 33 C and the organism was successfully cultivated directly from the ulcer of the last patient In its nutritive requirements the organism is fastidious to a degree comparable with the tubercle bacillus

In Vitro Cultivation of Rat Leprosy Organism Close resemblance of rat and human leprosy makes rat leprosy a valuable tool for understanding the pathogenesis of human leprosy Similarity of pathologic manifestations of both diseases has prompted many attempts to culture acid fast bacteria found in lesions characteristic of both diseases but these attempts have not been clearly successful because of failure to reproduce the disease in animals from administered subcultured material Rivka Ashbel and Alexander Poljakoff[7] (Hebrew Univ Jerusalem) report cultivation of the rat leprosy bacterium with identity of the culture confirmed by induction of typical lesions in rats

Previous studies had indicated that metabolic activity of both bacteria and leproma was feeble (low oxygen consumption and immeasurably low aerobic or anaerobic glycolysis as determined by acid formation) It was therefore decided to attempt to grow the rat leprosy bacteria in comparatively simple mediums allowed to undergo gradual spontaneous desiccation under conditions in which prolonged observation was possible

Four egg slants were inoculated with leproma material and kept for a long period at room temperature By 269 days after inoculation tubes were dry and normal saline was added Smears prepared from one tube and stained by Ziehl Neelsen stain revealed a few acid fast bacteria By 510 days after inoculation more saline was added and the same tube re examined Many bacteria mostly in groups were seen on smear Subcultures were made on

(7) J I f ct D 83 79 8 Nov D 1948

suggest the advisability of making a Ziehl Neelsen preparation It is also insufficient to assume that a tuberculous infection is present because acid fast bacilli are found *or in an area of endemic leprosy to make a diagnosis* of leprosy without further differential investigation

In treatment fomentation and most active measures aggravated the condition The simplest dressings i e, saline were least disturbing The only effective measures were wide excision followed when vigorous granulations were present by skin grafting and centripetal elastic sponge pressure and application of simple lotions After granulations developed presence of numerous mycobacteria in surface exudate in no way hindered success of skin grafting an experience in keeping with observations by plastic surgeons regarding other bacteria which in such circumstances cease to be effectively pathogenic

In three cases in which detailed laboratory studies were made material from ulcers infected rats and mice but not guinea pigs In rats characteristic lesions were produced including ascites cutaneous edema and ulceration and the disease was transferable indefinitely from rat to rat Similarity of lesions in animals and of morphologic and cultural characters of the strains confirmed the opinion that organisms isolated from each of the patients were of the same species Morphologically the organism resembles human tubercle bacillus It is gram positive if methyl violet stain is warmed it stains brilliantly by Ziehl Neelsen method and is strongly acid fast Evidence that this acid fast bacillus is not one of the well known mycobacteria follows from study of pathogenicity of the genus Human or bovine or vole tuberculosis was not produced in guinea pigs Avian tuberculosis was not produced in a cockerel and lesions were not produced in cold blooded animals Reservoir of the organism and method of transfer to man has still to be elucidated

The fact that lesions in man were on the skin of extremities and those in rats in the scrotum or on the tail and limbs suggested that the organism might require a

ward and Joseph E Smadel[8] Chloromycetin® is a crystalline substance relatively insoluble in water but well absorbed from the gastrointestinal tract Despite bitter taste it is well tolerated orally and this method of administration produces blood levels of the drug comparable to those after parenteral administration

The drug was given 15 patients with Rocky Mountain spotted fever The patients were observed throughout the remainder of the febrile course and convalescence in the hospital Ten patients were under age 16 Important clinical diagnostic criteria included history of exposure to ticks (found in 12 patients) persistent fever since onset characteristic rash and other suggestive abnormalities which included severe headache mental dulness torpor or delirium splenomegaly tarsal conjunctivitis slight periorbital edema and photophobia None of the patients had a history of any other type of infection capable of producing the clinical picture Laboratory confirmation of diagnosis was accomplished by one or more methods In some diagnosis was confirmed by injecting patients blood into guinea pigs and performing complement fixation tests on guinea pigs serum after the animals had a temperature of over 104 F for three consecutive days Blood was drawn before treatment and on the average of four times during therapy for guinea pig inoculation In other patients diagnosis was proved by agglutination tests for Proteus OX19 performed before treatment and thereafter every four days during hospitalization Titers higher than 1 160 were considered positive In others diagnosis was confirmed by complement fixation test against antigen of Rickettsia rickettsii Titers above 1 10 were accepted as positive Complement fixation reactions were positive in all patients Agglutination tests were positive in 14 and guinea pig inoculations positive in 7

Chloromycetin® was administered orally Except for the first two patients and one other in whom gavage

(8) A I t M d 29 656-653 O t ber 1948

flooded egg slants and 38 days later a random tube showed numerous acid fast bacteria and macroscopic colonies Subcultures then made on semisolid agar medium showed numerous acid fast bacteria 24 hours later and subculture from the semisolid medium showed macroscopic growth in six days

In all 76 tubes of various mediums were inoculated at different times with material from 10 rats previously in fected from other rats Of these 76 tubes 66 proved posi tive Minimal period requisite for definite multiplication was 50 days Ten tubes showed no multiplication until 1½ years had elapsed Impression was gained that growth was fastest on semisolid a ar plus rabbit blood Once good cultures were obtained it was simple to obtain rich subcultures in a wide variety of routine mediums

Proof that these acid fast bacteria were rat lepro y organisms was established by experiments in which 100 rats were given injections of the primary cultures and various subcultures Of 53 of these rats killed from 2 days to 1½ years after inoculation 22 were positive Of 47 animals killed one to three years after inoculation 9 showed various neoplasms and 10 had typical rat leprosy These results suggest that other workers results would have been clearer had both their cultures and subsequent animal inoculations been allowed to proceed much longer

During preparation of this paper opportunity arose to compare these findings with those of Wells for the vole acid fast bacillus and a number of points of similar ity of this organism to the rat leprosy organism were noted The rat leprosy bacterium may be closer to the vole bacillus than to the well established human and bovine types

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ROCKY MOUNTAIN SPOTTED FEVER

Treatment of Rocky Mountain Spotted Fever with Chloromycetin* is reported by Maurice C Pincoffs Ernest G Guy Leonard M Lister Theodore I Wood

hours after the initial dose Average duration of fever after initiation of therapy was about 2 2 days

A few patients vomited after the first or second dose but not thereafter Diarrhea and jaundice were not observed Repeated studies of urine and blood during treatment failed to show any evidences of drug toxicity

For comparison the records of 46 patients admitted before chloromycetin® was available were studied Figure 7 gives data on duration of fever in both groups

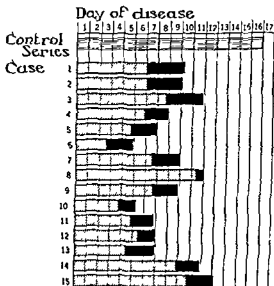
[Chloromycetin® and aureomycin (see following article) seem unquestionably superior to para aminobenzoic acid in rickettsial infections —Ed]

Aureomycin Therapy of Rocky Mountain Spotted Fever is reported by Sidney Ross Emanuel B Schoenbach Frederic G Burke Morton S Bryer E Clarence Rice and John A Washington[9] Because of the known antirickettsial activity of aureomycin it was administered to 13 patients with Eastern type Rocky Mountain spotted fever Three doses each containing 2 5 mg aureomycin/kg were given at hourly intervals at onset of therapy Thereafter the same dose was given every two hours until temperature had been normal approximately 48 hours Then the interval between doses was changed to four hours Period of therapy varied from 4½ to 9 days No exacerbations of fever were noted after discontinuance of the drug Total dosage varied from 2 3 to 16 3 Gm and averaged 9 5 Gm Though optimal dose of aureomycin in spotted fever has not been determined the authors believe that daily dose should be 30 60 mg /kg body weight orally No significant toxic reactions occurred Nausea and vomiting during the first two days in four patients was mitigated in two by simultaneous administration of aluminum hydroxide

Rapid defervescence and striking clinical improvement occurred in all patients Most patients were toxic irritable anorexic and lethargic before treatment Within 24 48 hours after starting aureomycin children were much

(9) J A M A 138 1213 1 16 D 25 1948

was necessary initial dose was approximately 75 mg./kg estimated weight and was administered in two or three parts at about one hour intervals Thereafter 0 25 Gm was given every three hours to children under 16 and 0 5 Gm to older patients In all but the first four pa



F g 7—D t n of fe e in 15 ses f Rocky Mou ta n p tt d f r treated w th hl omy t n® comp d w th 46 c t ol h o tal l e er ge d rat on n c t ols d agon l l du at on b f th rapy bl k a a durat on ft th apy (C urt y f P n offs M C *et al* An Int. Med. 29 656 663 O t ber 1948)

tients the drug was discontinued when temperature had remained below 100 F rectally for 24 hours

Clinical improvement occurred in all patients within the first 24 hours but was not striking until the second day when headache mental dulness etc were definitely relieved After initiation of treatment eruptions did not spread and by the end of the second day they had re ceded In most patients convalescence was established by the third day Temperature was normal within 76

development during convalescence of agglutinins for the OX K strain of Bacillus proteus Statistical data on the treated and on an untreated (control) group are summarized in the table

All 25 patients in the treated group received an initial

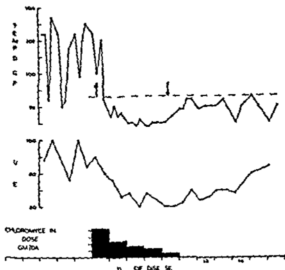


Fig 8 —Response of patient with scrub typhus to chloromycetin (Courtesy of ... 108 160 161 Aug 13 1948)

oral dose of about 50 mg chloromycetin®/kg body weight and then 0 2-0 3 Gm by mouth every two to four hours Initially treatment was continued until at least the twelfth day after onset of illness Duration of treatment was gradually shortened and the last seven patients were given the drug for only 24 hours Responses

more active and alert and appetite and an interest in the surroundings returned In 11 of the 13 course of the disease was so promptly altered that no supportive treatment was required

Results in these patients were contrasted with those in 17 patients treated with para aminobenzoic acid (PABA) in 1946 and 1947 and in 30 patients before this period who were given no treatment Death rate without treatment was 10 per cent but no deaths occurred in patients given PABA or aureomycin Average number of days of fever after treatment was begun was 6 3 in patients given PABA and 2 3 in patients given aureomycin Patients given PABA were hospitalized 12 days (average) and those given aureomycin 8 days Incidence of complications including pneumonia myocarditis and parotitis was 26 6 per cent among untreated patients 17 6 per cent among those given PABA and 0 among those given aureomycin It was concluded that aureomycin was superior to PABA in treatment of Rocky Mountain spotted fever Though it had been generally agreed that PABA was of no benefit unless treatment was instituted during the first week in two patients given aureomycin treatment was not instituted until the eighth day of illness In addition aureomycin appears relatively nontoxic in contrast to PABA which has produced leukopenia and liver and kidney damage

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SCRUB TYPHUS

Chloromycetin* in Treatment of Scrub Typhus Joseph E Smadel Theodore E Woodward Herbert L Ley Jr Cornelius B Philip Robert Traub R Lewthwaite and S R Savoor[1] treated 25 person with scrub typhus with chloromycetin* Diagnosis was proved in each instance by recovering Rickettsia tsutsugamushi from blood taken before treatment or by demonstrating

(1) Science 108 160 161 Aug 13 1948

durated area 2-6 cm in diameter Such hypersensitivity could first be demonstrated between the second and third month following convalescence When the test was repeated four months after the first test reaction was usually more pronounced

The same dose of vaccine was given to 75 volunteers Complement fixing antibody titer was determined on their blood before and four weeks after inoculation A significant rise of complement fixing antibodies resulted from this vaccination

Index of susceptibility to mumps is well demonstrated by use of the vaccine Rise of complement fixing antibody titers after vaccination suggests that the vaccine may be of value in prophylaxis against mumps There is no evidence that this immunity is permanent No untoward reactions followed vaccination Follow up studies of the 400 subjects will be necessary

[Killed virus will probably not confer life long protection against mumps therefore even if this vaccine does give temporary immunity the problem will be to determine when it should be used As is true of measles chickenpox and rubella it may be preferable to have mumps in childhood when manifestations are usually comparatively mild.—Ed]

Isolation of Mumps Virus from Human Beings with Induced Apparent or Inapparent Infections Gertrude Henle Werner Henle Katherine K Wendell and Philip Rosenberg[3] (Univ of Pennsylvania) isolated mumps virus from the saliva of 13 of 15 children to whom the virus was administered Parotitis developed in only six orchitis alone occurred in one and the others showed no clinical evidence of mumps

All patients with parotitis excreted virus in the saliva beginning 11 15 days after exposure and 2-6 days before onset of clinical signs of disease Virus was found until the fourth day of illness The patient with primary orchitis without parotitis excreted virus in the saliva 15 days after exposure and 10 days before illness Virus was excreted by six of the eight children classified as having

(3) J Expe M d 88 23 232 A gu t, 1948

DATA ON TREATED AND UNTREATED PATIENTS WITH SCRUB TYPHUS

DATA	TREATED GROUP	UNTREATED GROUP
No of patients	25 (18 M 7 F)	12 (M)
Days after onset therapy was begun	3 11 av 6 2	—
Last febrile day of illness	4 12 av 7.5	13 29 av 18 1
Duration of fever (hr) after therapy was begun	10 96 av 31 0	—
Day of discharge from onset	9 28 av 19.2	17 53 av 30.7
Complications	0	Parotitis 1 pneumonia 1
Deaths	0	1 on 17th day
Mo of onset	Mar Apr	Feb Mar

with the short regimen were just as satisfactory as with longer periods of therapy The typical response of one patient a youth aged 19 weighing 140 lb is shown in Figure 8

Chloromycetin® appreciably lessened morbidity from scrub typhus and can be used in the home

MUMPS

Mumps Vaccine Studies on Human Volunteers were conducted by Hascall H Muntz Horace M Powell and Clyde G Culbertson* (Indiana Univ) Vaccine was prepared from heat killed virus from rabbits inoculated with virus propagated on chick embryos Its strength was determined by complement fixation and hemagglutination inhibition tests done on blood of rats previously inoculated with the vaccine

Vaccine 0 1 cc containing 2 complement fixing units was placed intracutaneously on flexor aspects of fore arms of 400 human volunteers and the areas were observed 24 36 hours later Reaction was considered positive if there was an area of edema larger than 1 cm plus a zone of erythema larger than 2 cm Typical local reaction in persons who had had mumps and had a significant complement fixation titer was an erythematous in

( ) J Lab & Clin Med. 34 199 208 February 1949

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(3) J Exper Med 88 223 232 Aug 1948

inapparent infections and was first detected 15 16 days after exposure and continued 1 9 or more days

Data collected in these experiments confirmed deductions based on previous epidemiologic studies Incidence of inapparent infections in mumps has been estimated to be 30-40 per cent Patients show complement fixing antibodies for mumps despite the fact that they have had no clinical signs of infection

The results of virus isolation showed that the period of communicability of patients with parotitis began 11 15 days after exposure and extended to the eighteenth or nineteenth day Even patients without clinical signs of the disease may spread the virus however

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MEASLES

Pneumonia of Measles is discussed by Louis Weinstein and William Franklin[4] (Boston) Although measles is common it is rarely dangerous unless complicated by suppurative otitis media encephalitis or bronchopneumonia Estimates of bronchopneumonia incidence in measles have varied from 22 6 per cent *among* hospitalized patients to 6 per cent among the unhospitalized Among 163 cases of measles reviewed by the authors incidence of pneumonia was 25 1 per cent There was x ray evidence of pneumonia in 21 of 41 patients in whom the diagnosis was made In the remaining 20 diagnosis was based on presence of respiratory difficulty accompanied by cyanosis tachycardia leukocytosis fever or abnormal physical findings in the lungs *Underlying disease of* serious nature was common in patients who had pneumonia during measles Mongolian idiocy was present in two spastic paralysis in one lipoid nephrosis in two severe anemia in three and eventration of the diaphragm in one History of frequent respiratory infection was common and six patients had had pneumonia previously

(4) Am J M Sc 17 314 324 Ma h 1949

In half the patients pneumonitis was first evident early in the eruptive stage of measles in seven it oc curred when the rash was fading and in a few after rash had disappeared Five had lung involvement before eruption appeared

In almost half the patients with pneumonia and measles the only x ray abnormality was hilar and peri bronchial infiltration Usually this was interpreted by the roentgenologist as bronchopneumonia but occasion ally interpretation was acute respiratory infection with out pulmonary parenchymal involvement

White cell counts were normal or moderately decreased with rise in number of mononuclear cells in uncompli cated measles Early stages of pneumonitis were accom panied by rise in neutrophilic granulocytes and con valescence brought an increase in number of mononu clear cells

Contrary to previous reports beta hemolytic strepto cocci were found in throats of only seven patients the most common organisms recovered being alpha hemo lytic streptococcus and nonhemolytic Staphylococcus aureus Hemolytic Staph aureus was found in 25 per cent and was considered of great importance because it is a known common cause of bronchopneumonia in early childhood Hemophilus influenzae was found in 25 per cent but pneumococci were not found in any

Penicillin was given as soon as pneumonia was de tected without waiting for establishment of etiologic di agnosis Of the entire group 50 per cent were afebrile after 48 hours treatment 70 per cent after 72 hours and all six days after start of treatment Pleural effusion occurred in two patients in one chest fluid was sterile and Staph aureus empyema occurred in the other

Despite severity of the disease in some patients there were no deaths The favorable results leave little doubt as to value of penicillin in treatment of pneumonia com plicating measles

[The bacteriology of measles pneumonia has not had much

study The frequent presence of Staphylococcus aureus and absence of pneumococcus in these cases is of interest.—Ed]

Appendical Lesions in Prodromal Stage of Measles are reported by Morris A Simon and Harry C Ballon[5] (Montreal) Large multinucleated giant cells resembling megakaryocytes have long been known to occur in tissues other than the skin during the prodromal stage of measles These cells known as Warthin Finkeldey giant cells have been found in the lung tonsils and lymphoid tissue adjacent to the appendix

The authors studied four children aged 7 10 who were operated on during the prodromal stage of measles because they were thought to have appendicitis The appendix was acutely inflamed in two patients in the others mesenteric adenitis appeared to be present Typical measles rash appeared three to five days after operation in these patients

Microscopic study of lymphoid tissue adjacent to the appendixes revealed typical Warthin Finkeldey giant cells in all four patients In three of the four demonstration of these typical cells permitted diagnosis of measles before the rash appeared Warthin Finkeldey giant cells are thought to result from fusion of lymphocytes and are considered pathognomonic of measles

Though it is well known that mesenteric adenitis may accompany measles appendicitis may also occur during measles and warrants appendectomy

[Now and then a pathologist has the satisfaction of predicting that a measles rash will appear in a young patient who has just undergone an appendectomy —Ed]

Measles Encephalitis Emanuel Appelbaum Vera B Dolgopol and Joseph Dolgin[6] (Willard Parker Hosp New York City) reviewed records of 74 patients with measles encephalitis myelitis or both from May 1936 to June 1946 Autopsies were performed on 7 patients and follow up studies were available on 33

The etiology of measles encephalitis is unknown but

(5) Am. J Clin. Path 18 796-804 October 1948
(6) Am. J Dis Child. 7 25-48 January 1949

it has been suggested that the nervous system is invaded by the measles virus that measles activates a virus dormant in the nervous system or that there is an allergic response of the central nervous system to the virus of measles

Perivascular loss of myelin believed to be characteristic in the histologic picture of measles encephalitis was observed in only four patients and all of these had had the disease three days or longer Cellular infiltration of walls of small and medium sized veins of the brain was found in all cases at autopsy Infiltrating cells were predominantly lymphocytes Such cellular infiltration has only rarely been mentioned previously in literature on measles encephalitis but it has been mentioned in encephalitides complicating smallpox vaccination and smallpox Venous thrombi were not constant or important observations in the authors patients Significant changes in ganglion cells were observed in all patients Cellular infiltration of the meninges was present in four and in three early cases was limited to a few sulci of the cortex Infiltrating cells were lymphocytes in all except one patient where polymorphonuclear forms were also present It is concluded that measles encephalitis is primarily an inflammatory disease of the central nervous system in which myelin degeneration occurs when the disease persists three days or longer Consequently the term measles encephalitis is preferred to measles encephalopathy

Incidence of encephalitis in measles is slightly less than 1/1 000 It occurred in 86 1 per cent of the authors patients between the second and sixth day after eruption Disease was often ushered in dramatically with coma convulsions or both Temperature often reached 104 or 105 F with onset of encephalitis Pulse was rapid and respiration often irregular Stiffness of the neck with Kernig s Brudzinski s and Babinski s signs was common In some patients onset of encephalitis was gradual with drowsiness irritability and often vomiting In a few

patients illness started with excitement and delirium Temperature was almost always elevated but pursued no characteristic course

Clinical signs varied with the area involved and almost every symptom and sign of central nervous system disease was encountered Consciousness was nearly always disturbed Restlessness and irritability were common Some patients were extremely noisy and talkative and occasionally psychosis was encountered Reflexes were variable and ankle clonus occurred frequently Other common abnormalities included pupillary disturbances blurring or atrophy of optic disks extra ocular muscle paralysis nystagmus facial palsy facial masking oculogyric crises paraplegia and hemiplegia

Mortality rate was 9 5 per cent Of patients who recovered 56 8 per cent were discharged without neurologic or other detectable abnormalities Of 33 patients followed longer than four months 28 were observed for periods exceeding two years Thirteen had no residual symptoms The remaining 20 had various sequelae the most common of which were psychosis mental retardation paralysis and personality deviation Treatment of measles encephalitis is at present entirely symptomatic Human gamma globulin needs further clinical trial for evaluation as a therapeutic agent in this disease

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NEWCASTLE DISEASE

Outbreak of Newcastle Virus Disease in Tuscarawas County, Ohio, is reported by Thomas F McGough[7] (New Philadelphia) Three days after chicken was served by the N family their child 6 had sudden nausea vomiting fever (101 F) malaise anorexia abdominal pain lumbar pain and headache All symptoms disappeared in two days Five days after the chicken was served an adult member of the family was seized abruptly with

(7) Oh State M J 45 5 6 J ary 1949

headache nausea vomiting diarrhea abdominal cramps lumbar pain and marked weakness The e symptoms also disappeared in two days leaving only weakness which persisted a week Two days after chicken from the same source (purchased locally but shipped from out of state) was again served in the household the other adult member of the family had sudden onset of headache nausea and diarrhea followed by generalized myalgia and weakness and temperature of 101 F Again symptoms disappeared within 48 hours leaving only weakness for a few days

Eating these chickens was the only known contact with poultry that the family had had for several weeks Symptomatology and circumstances were so suggestive of Newcastle virus disease that blood specimens from the two adults were sent to a U S Public Health Service laboratory for a neutralization test against Newcastle disease virus Both samples were reported as positive Because several other persons in the community had had practically identical symptomatology at approximately the same time their blood samples were forwarded for examination Six of the seven samples sent were reported positive Bacterial contamination occurred in the remaining sample All these patients reported eating chickens probably of local origin None were poultry raisers

Though generalizations cannot be drawn safely on so few cases it appears logical to state that the incubation period for human Newcastle virus disease may be as short as 2½ and at least as long as 5 days

[A new virus disease is occurring in the United States We still lack detailed clinical description but apparently it may take the form of a grippe-like illness may resemble poliomyelitis in children or may cause pneumonitis —Ed]

Clinical Features of Summer Disease (Three Day Fever) Apparently of Virus Etiology In the summers of 1946 and 1947 C H Webb S Geo Wolfe and Verre Simpson[3] (Shreveport La) observed outbreaks among

(3) New Orleans M & S J 101 49 256 December 1948

children of an acute illness which lasted three to five days and then cleared as mysteriously as it developed The ill ness appeared similar to a pandemic in a number of lo calities throughout the United States and generally was called three day fever The authors analyzed its clini cal features in 48 children

Onset was typically abrupt with sudden high fever headache and malaise Temperature was usually 101 104 F throughout the illness though a few children had one febrile day followed by one to three days of normal temperature and then a secondary rise for two to four days Headache was a spontaneous complaint in all 24 children over age 5 and in a number of those in the 3 5 year age group Generalized myalgia occurred in about one third Respiratory symptoms were unusual and gas trointestinal symptoms minimal being limited in most cases to temporary anorexia After two to four days (average 3 3 days) temperature subsided rapidly and the child was well

Physical findings were few Mild to moderate injection of the pharynx was frequent but not invariable Pulse and respiratory rates were proportionate to temperature elevation Generally the children did not seem as pros trated or toxic as might be expected with the degree of pyrexia Leukocyte counts were normal to low being under 10 000 cells/cu mm in every instance

After the foregoing was written a report from the U S Public Health Service Laboratory Montgomery Ala suggested on the basis of serum neutralization tests that the virus of pneumoencephalitis of fowl (New castle disease) was the agent responsible for similar epi demics occurring among children and occasionally in adults in Tennessee and Alabama in 1947 and 1948 Serums from several children in this series were reported by the same laboratory to show positive neutralization tests Conclusive proof by isolation of *Newcastle* virus from a human being has not been accomplished

Presence of Neutralizing Antibodies of Newcastle Disease Virus in Human Serums In 1926 a highly infectious and fatal disease of fowls was first recognized in Dutch East Indies and at Newcastle upon Tyne England A year later a filtrable agent was isolated and designated Newcastle disease virus (NDV) Similar outbreaks among poultry have since been described in various parts of the world In California in 1941 and 1942 a respiratory central nervous system disorder of chickens was recognized and designated avian pneumoencephalitis By means of the serum neutralization test the serologic similarity of the virus of this disease to that of British Newcastle disease was established and presence of the disease was demonstrated throughout the United States

Beatrice F Howitt Lindsay K Bishop and Robert E Kissling[9] (Montgomery Ala) describe accumulated evidence which indicates that the poultry disease has become significant to man in the United States and that human manifestations follow closely those described for the avian disease either respiratory or neurologic symptoms or both They examined serum from various groups of children in Alabama and Tennessee who had a mild central nervous system infection of short duration and without sequelae Because of frequent contact with chickens and absence of antibodies for the common neurotropic viruses serum neutralization tests were done against the virus of pneumoencephalitis (Newcastle disease) of fowl Serums of 12 of 15 Tennessee children with the syndrome were positive to NDV those of 78 children without the syndrome were negative In rural Alabama serums of 8 of 10 persons with the syndrome had definite neutralizing antibodies for NDV In several of the positive cases there was a history of contact with chickens During work with the virus in the laboratory an acute influenza like infection developed in six members of the staff Antibodies in high titer against NDV were found in their serum

(9) Am J P b Health 38 1263 1272 S pt mb 1948

In general this syndrome is of sudden onset and follows an abrupt febrile course recovery is rapid without paralysis or other sequelae Because children are often affected and manifest certain poliomyelitis like symptoms the disease is often reported as poliomyelitis Other patients may have meningeal irritations and the disease may be called meningitis Others show pneumonitis *particularly adults*

Although conclusive proof is lacking without isolation of a virus results of serum neutralization tests suggest that the virus of pneumoencephalitis (Newcastle disease) of fowls is the etiologic agent responsible for this varied syndrome In immature birds and in children neurologic symptoms predominate whereas in adult chickens and adult humans respiratory symptoms are more pronounced

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COMMON RESPIRATORY DISEASES

Natural History of Common Cold Ignorance of the natural history of the common cold has impeded attempts *to prevent or cure it It often appears that a cold is* caught by contact with an infected person although it also seems to be acquired through getting the feet or body wet or chilled C H Andrewes[1] (Harvard Hosp Salisbury) reports experience of a research unit established by the British Ministry of Health in 1946 to obtain information about epidemiology of the common cold Study was conducted in a hospital established during the war which consisted chiefly of 22 prefabricated huts and other outlying buildings Huts were divided into two flats each of which accommodated two persons during the 10 days confinement for the experiment

In 2½ years of the study there were 899 visits from volunteers (not 899 persons since many came back two or three times) The subjects were used almost wholly

(1) Lancet 1 71 75 Jan 8 1949

as indicators of presence of a cold producing agent in test materials For instance after attempted cultivation of a virus in eggs material from the egg was tested on volunteers to see whether the virus survived Volunteers arrived on Wednesday and for 10 days were confined so that they came in contact with only one other person During this period meals were placed outside their doors and they were allowed walks but requested to stay 30 ft away from people they met Routine clinical and x ray (chest and sinus) examinations were done and subjects observed for three days in case any should already be incubating a cold All not free from signs and symptoms and their partners were excluded from the main study On Saturday morning intranasal inocula tions of 0 5 ml fluid were run into each nostril with the patient supine Sheets were provided for daily recording of symptoms by volunteers and patients were visited once daily by a clinician and matron for clinical evalua tion Most trials included instillation into some subjects of control supposedly inert material Neither volun teers nor clinicians knew which patients were receiving control and which supposedly infectious material

Whether the common cold is an entity has been de bated Certainly several infections produce symptoms which most people call colds In this study for exam ple mild symptoms of a cold were produced in some sub jects by inoculating influenza A virus attenuated for man by long continued cultivation in fertile eggs It appears likely therefore that in normal circumstances influenza virus can produce mild coldlike symptoms in some relatively immune people Other workers have re ported that an agent producing atypical pneumonia in some people gave rise in others to symptoms of a com mon cold On the other hand the authors stored at —76 C two strains of cold producing agents for many months and with these and materials obtained by serial passage of them through man produced a disease with only a moderate range of variation in signs and symp

toms Incubation period was usually two or three days with range of one to six days Signs and symptoms included some roughness or soreness of throat usually at onset nasal discharge malaise and headache Fever and postnasal discharge were rare and cough developed in only about one third of patients In many subjects receiving known infective material symptoms suggestive of colds appeared but were soon aborted Since such symptoms were not reported by controls it is likely that many colds abort spontaneously Since symptoms in experimentally produced colds were much the same as those characteristic of spontaneous colds which developed during the quarantine period Andrewes and co workers believe that though other organisms may produce similar syndromes most of the total number of colds are one disease

The syndrome described was produced in 60 per cent of volunteers Such colds were transmitted in series through four persons and are almost certainly due to a multiplying agent probably a virus Size of the virus was estimated by filtration through Elford s gradocol membranes Results suggested that the common cold virus is considerably smaller than the influenza virus

Since the first object of this study was to find a laboratory tool with which to study virus of the common cold cultivation of virus in fertile hens eggs was repeatedly attempted No evidence of successful cultivation was obtained nor even of survival for one passage Failure to cultivate a cold virus in fertile eggs in this study contrasts with other workers previously reported success Andrewes suggests that possibly other workers were dealing with an infectious agent different from the one involved in his group s study Attempts to pass infection to many experimental animals including rabbits guinea pigs rats mice cotton rats hamsters ferrets kitten pigs and hedgehogs were also unsuccessful

Though many workers have failed to find bacteria in

cold secretions some bacteriologists believe that colds may be caused by pneumococci or other bacteria This argument might be countered by inducing colds by means of bacteria free filtrates of washings from patients with such infections

These studies confirm the clinical opinion that colds are especially infectious in early stages When nasal washings were made 12 24 36 and 48 hours after inoculations and these washings inoculated into volunteers no takes were detected in 12 hour washings but good takes were obtained with 24 36 and 48 hour specimens indicating that the virus was present and probably plentiful 24 hours before symptoms of cold developed

The fact that 40 per cent of patients proved resistant during this experiment and yet in most instances had colds at other times during the year suggests that resistance to colds depends on time elapsed since the last cold

Among pairs of volunteers studied there was a tendency for both to contract a cold or for both to be resistant and in only a small percentage did one contract a cold and the other not Members of these pairs were usually friends who had lived in the same environment at home It is suggested that close associates might tend to be in the same phase of acquisition temporary carriage and ultimate loss of virus from the nose

Andrewes concludes that colds result from a virus which in a large community is constantly passing from one person to another usually causing no symptoms or only abortive ones and causing real colds only in victims whose resistance is temporarily diminished Such persons disperse virus in great quantities Few persons harbor virus long so in isolated communities it usually soon dies out

[Andrewes and his associates have begun a thorough long term study of the common cold and their observations can be counted on to provide solid information about the disease Progress will necessarily be slow as long as human volunteers must be depended on as experimental subjects —Ed]

Appendicitis and Upper Respiratory Infection Report of 18 Cases at Sea George L Calvy (M C USN) reports that during the first six months of a one year period aboard a naval vessel in the South Pacific there were no cases of appendicitis After this an abdominal syndrome clinically indistinguishable from acute appendicitis was seen frequently in association with virus type colds Eighteen cases occurred in three months coinciding strikingly with three epidemic waves of upper respiratory infection The abdominal syndrome appeared only among ship s company sparing both passengers and officers Colds were also most frequent among ship s company

The upper respiratory manifestation consisted of nasopharyngitis accompanied by a thin colorless mucoid secretion and often associated with mild to moderate malaise and low grade fever All but 2 of the 18 men cited head cold as a forerunner of abdominal distress

Twelve patients were operated on after 12 24 hours observation The others exhibited improvement were treated medically and later were discharged with a diagnosis of mesenteric lymphadenitis Abdominal pain localizing in the right lower quadrant fortified by the finding of localized tenderness and an essentially normal urinalysis in the absence of pulmonary pathology favored the diagnosis of acute appendicitis

All appendixes removed showed evidence of acute inflammation with conspicuous vascular engorgement and swelling Free peritoneal fluid was present in four cases plastic fibrinous exudate was noted seven times enteroliths were present in four appendixes but without demonstrable evidence of causing primary obstruction and old adhesions and regional lymphadenitis were noted three times

These data suggest that at least in some circumstances there may be a close relation between an epidemic type of respiratory infection and onset of acute appendicitis

(2) Ann Int Med 28 998 1007 May 1948

Handkerchiefs in Transfer of Respiratory Infection have received less attention than they deserve according to K. K. Dumbell, J. E. Lovelock and L. J. Lowbury.[3] They therefore conducted experiments to determine the numbers of bacteria carrying particles which could be shaken from used handkerchiefs and the reaction of these particles to aerial disinfectants.

Sterile cotton handkerchiefs about 1 ft. square were issued to volunteers and collected after two days' use. They were dried in a quiet, dust-free room and then shaken one at a time by being held in the air stream of a blower. Suspended particles were sampled immediately by a slit sampler onto nutrient agar plates enriched with horse serum.

Average number of bacteria-carrying particles obtained by prolonged agitation from 211 handkerchiefs was 136 000. On the average 15 000 and occasionally as many as 50 000 particles were distributed from a dry handkerchief by gentle manipulation. The latter figures are even more significant in view of the fact that these particles, although airborne, are almost completely resistant to action of the best available aerial disinfectants. Weight of particles was eight times that of droplet nuclei from the mouth and may therefore carry a correspondingly larger content of bacteria.

The authors believe that use of handkerchiefs is probably the most important single action, except bed making, in contamination of air with micro-organisms from the respiratory tract.

Penicillin Treatment of Streptococcic Pharyngitis. Critical appraisal of any treatment demands establishment of strict control groups and accurate delineation of the natural history of the disease in question. Survey of the current literature discloses no study of streptococcic pharyngitis in which a strict control group was established without regard for severity of the presenting illness. An epidemic of streptococcic pharyngitis at a large

3 ... ... 183-185 July 31 1948

permanent army post allowed J Philip Loge and Edwin D Kilbourne[4] (Ft Monmouth N J) to make a systematic study of effects of treatment on its course The epidemic was caused by group A hemolytic streptococci largely types 19 and 23

During 60 days in the spring of 1947, 184 patients received a preliminary clinical diagnosis of streptococcic pharyngitis and were placed in special study groups on admission It has been implied that the definitive diagnosis of streptococcic pharyngitis depends on demonstration of antistreptococcic antibodies during convalescence However 10 20 per cent of scarlet fever patients may fail to exhibit an antibody response and penicillin treatment of either scarlet fever or streptococcic pharyngitis may prevent the usual antistreptolysin respon e Hence the value of this important criterion for diagnosis of streptococcic disease is somewhat limited For final inclusion of patients in this study the following criteria were required (1) fever over 100 F on day of admission (2) predominating growth of beta hemolytic streptococci on initial throat culture and (3) admission total leukocyte count over 10 000 cells/cu mm

Application of the criteria plus loss of patients by transfer and incomplete laboratory data reduced the series from 184 to 127 patients The high proportion of patients in the untreated group who exhibited a significant antistreptolysin rise is evidence of the accuracy of the preliminary diagnostic impression The 127 patients were divided into three groups Those in the untreated group received symptomatic therapy in the form of hot saline gargles or irrigations obligatory bed rest for three days and codeine when necessary The rest received the symptomatic therapy outlined plus penicillin One group received penicillin in a single daily injection of 300 000 units in aqueous solution for six or seven days The other group received 20 000 50 000 units of penicillin every three hours for four to seven days

(4) A n I t Med 9 698 714 October 1948

Hemolytic streptococcic pharyngitis in these patients was differentiated clinically from other endemic respiratory tract diseases by its more abrupt onset primary complaint of sore throat and greater prostration in its victims A surprising number of patients (82 9 per cent) complained of headache Fever was usually present on admission and exceeded 102 F in almost 70 per cent A cardinal sign was the cautious manner in which patients opened their mouths for examination illustrating dramatically the soreness of the pharyngeal and peripharyngeal tissues Pharyngeal injection was present in all patients Obvious pharyngeal edema occurred in three fourths of patients and was a valuable diagnostic sign Confluent exudate was observed in only 60 per cent of patients Cervical lymphadenopathy was frequent and was most often in tonsillar nodes

Average fever duration was similar in the three groups though the course tended to be slightly shorter in penicillin treated patients Most patients regardless of treatment had no symptoms by the fourth day The group given frequent injections of penicillin had no pyogenic complications whereas such complications developed in two patients in each of the other groups Rheumatic fever developed in two patients and arthralgia in one in the group given a single daily injection of penicillin and prolonged fever developed in one patient in the untreated group and microscopic hematuria in another whereas no such complications appeared in the group given penicillin every three hours All patients who had recurrence of infection had been given antibacterial therapy No relapses occurred in the controls Significant rise in antistreptolysin titer occurred in 84 3 per cent of untreated patients 63 8 per cent of those treated with large daily injections of penicillin and only 13 8 per cent of those given frequent injections of penicillin Treatment which suppresses formation of one streptococcic antibody may suppress production of others including the sensitizing antibody of rheumatic fever

Interference with antibody formation by penicillin is most logically related to early removal of the antigenic streptococcus Penicillin treatment greatly lessened incidence of positive cultures on the twenty first day whether administered daily or every three hours

[Additional evidence that penicillin therapy of acute streptococcic respiratory infection may prevent occurrences of rheumatic fever is given in this YEAR BOOK page 116 —Ed]

Gangrene of Feet and Hemolytic Anemia Associated with Cold Hemagglutinins in Atypical Pneumonia is reported by Richard M Carey James L Wilson and Joseph A Tamerin[5] (Harlem Hosp New York City) Cold hemagglutinins in titers above 1 32 rarely occur except in virus pneumonia They are usually active at temperatures below 25 C but occasionally are active at 37 C Many cases of hemolytic anemia several cases of pulmonary infarction and two cases of gangrene from these hemagglutinins have been observed Usually such patients have had hemagglutinins in high titer

Woman 31 was hospitalized for illness of two weeks duration first diagnosed influenza and then bronchitis A week previously she had passed dark urine and had noticed her toes were blue Examination revealed nothing significant except generalized rhonchi and cyanosis of the fourth and fifth left toes Dorsalis pedis pulse in this foot was palpable X rays showed density of the left lower lung Red blood cell count was 1 600 000 and hemoglobin 24 per cent Cross matching was impossible until blood was heated Cold hemagglutinin titer was 1 32 768 Spherocytes were present but results of Donath Landsteiner acid hemolysis heat resistance sickle cell *and cell fragility tests done later were all normal*

Cyanosis of the foot spread rapidly and before presence of cold hemagglutinins was suspected the foot was placed in ice Cyanosis spread to include the entire foot to a point 2 in above the ankle Dorsalis pedis pulsation was no longer detectable in the foot Two days later the right foot showed beginning gangrene of the distal ends of the four outer toes but dorsalis pedis pulse remained palpable No pain was present in the right foot but was severe in the left Pain diminished after left lumbar paravertebral blocks at the level of the second third and fourth lumbar vertebrae Figures 9 and 10 show

(5) Harlem Hosp Bull 1 53 J 1948

reported that marked hemagglutination within constricted peripheral vessels produces color and sensory changes simulating Raynaud's syndrome and that prolonged vasoconstriction and intravascular hemagglutination are followed by capillary thrombosis and irreversible ischemic tissue changes

Primary Atypical Pneumonia Report of Eight Cases with Autopsies is presented by Frederic Parker Jr Leslie S Jolliffe and Maxwell Finland[6] (Harvard Univ) Though fatal cases of primary atypical pneumonia are not rare there are few autopsy reports In the authors eight cases the clinical course was characterized by increasing respiratory embarrassment diffuse moist rales and transient areas of atelectasis but no definite signs of pulmonary consolidation Chest x rays revealed extensive miliary soft nodular densities and cold agglutinins were found in the serum Sulfonamides were not beneficial and oxygen gave only partial if any relief in later stages In only two patients was leukopenia present at any time and white blood cell counts over 15 000 occurred in six patients Red blood cell counts were normal except in two patients with acute hemolytic anemia Blood cultures were negative Sputum smears showed polymorphonuclear leukocytes and few bacteria Cultures showed predominantly alpha hemolytic streptococci and later staphylococci A significant titer of complement fixation for psittacosis was found in one of five cases and tests for Q fever were negative Duration of the disease was 13 days in two cases 31 days in one case and 17 24 days in the other five

Grossly the lungs were enlarged and increased in weight Congestion was apparent and there were scattered areas especially in the posterior and inferior portions in which crepitus was diminished Surfaces overlying atelectatic areas were sharply outlined and dark purple red (Fig 11) Cut surfaces showed a characteristic miliary nodular appearance (Fig 12) Nodules

(6) Arch Path 44 581 605 December 1947



F g 11 (t p) —P t w f l g h w g h ply d m t d da k f t l ta f l w l b l p l g y f f mphy m tou pp l bes. (Sh y wh t h ghl gh)
F g 1 (b tt m) —S m C os t f l g C f how m mall g y od l d d by d k g t d l g p hym M f tra h a d b h d ply t d (Wh t a h ghl gh)
(C y f P k F J m l A h P th 44 581 608 Dec mb 1947)

were 1 2 5 mm in diameter and were usually gray or yellow against a hemorrhagic background Tracheal and bronchial mucosae were hyperemic and covered with dark mucus Alveolar exudate was composed of desquamated alveolar lining cells and large mononuclear cells Both frequently contained phagocytosed material Swelling of alveolar lining cells was prominent but necrosis rare Interstitial infiltration for the most part composed of plasma cells was constant and conspicuous It was found in the walls of bronchioles around blood vessels and frequently in alveolar walls Bronchioles were usually intact Pleuritis occurred only in presence of secondary bacterial invasion Thrombi were frequent Organization of alveolar and bronchiolar exudate was common but not extensive Lesions in other organs were inconspicuous

[Opportunity to study tissues from eight fatal cases of primary atypical pneumonia may not again occur in a single pathology laboratory since we now seem to have an effective chemotherapeutic agent for this disease (see the next two articles) This study therefore has special value —Ed.]

Treatment of Primary Atypical Nonbacterial Pneumonia with Aureomycin. Emanuel B Schoenbach and Morton S Bryer[7] (Johns Hopkins Univ) administered aureomycin to 13 patients with well authenticated diagnoses of atypical pneumonia All but one were severely ill and all required hospitalization Penicillin and/or sulfadiazine given in adequate doses to nine patients had had no effect Aureomycin was administered orally was well tolerated and was relatively nontoxic Fever disappeared within 12 hours in two patients within 24 hours in seven within 36 hours in two within 48 hours in one and within 72 hours in one Clinical response was striking

Up to Jan 5 1949 18 completely studied patients had been treated with results similar to those described Cold agglutinins were present in 20 per cent and agglutination for Streptococcus MG was positive in 75 per cent No

(7) J A M A 139 5 0 Jan. 9 1949

specific causative agent was demonstrated These results seem sufficiently encouraging to warrant further use of aureomycin in treatment of primary atypical pneumonia

Aureomycin in Treatment of Primary Atypical Pneumonia Because atypical pneumonia cannot be differentiated clinically from Q fever or from psittacosis and because these two conditions have responded favorably to aureomycin Yale Kneeland Jr Harry M Rose and Count Dillon Gibson[8] (Columbia Univ) tried aureomycin in a patient extremely ill with atypical pneumonia Results were sufficiently encouraging to warrant further trial

Since the course of atypical pneumonia is unpredictable criteria were established for selection of cases in which the drug was to be used Patients were chosen who had cough fever pneumonitis normal leukocyte count and normal bacterial flora of sputum Before aureomycin was administered it was first determined that penicillin in full doses for at least 48 hours had no effect and that the condition was deteriorating at the time treatment was instituted

Ten patients with what was believed to be atypical virus pneumonia were given aureomycin orally in daily doses of 4 Gm divided into six hourly doses then reduced gradually on succeeding days Later patients were given initial doses of 1 5 Gm followed by 1 Gm every six hours Usually the drug was continued until temperature had been normal several days and the patient was substantially improved In 8 of the 10 patients cold agglutinins developed at the expected period

In nine patients temperature became normal 12-48 hours after the drug was instituted with corresponding clinical improvement In two patients treatment was discontinued at this time and what appeared to be a recrudescence of the disease took place In the other seven treatment was maintained and recovery was uneventful

No important toxic side effects of aureomycin were

(8) Am J M d 6 41 50 J a y 1949

noted It is suggested that aureomycin may have an antiviral effect against the agent which causes atypical pneumonia in man

[These two reports are convincing Aureomycin seems to be effective in a remarkable variety of pneumonias including pneumococcic Friedlander s staphylococcic tularemic Q fever primary atypical and psittacosis —Ed]

PSITTACOSIS

Ornithosis (Psittacosis) Review with Report of Eight Cases Resulting from Contact with Domestic Pekin Duck is presented by William Wolins[9] (Riverhead N Y) Psittacosis is a disease of parrots which is highly communicable to man Ornithosis is the name given similar *infections in birds other than parrots* The bird harboring the disease reported here is the domestic duck of which 7 000 000 are produced annually on Long Island

Infection is transmitted to the young bird in the nest by the parent Mortality of such infection is low and excretion of virus in droppings and nasal discharges ceases in most birds after several months Virus remains latent in spleen and other organs and may become activated by adverse environmental conditions Transmission to man usually results from inhalation of dust containing virus particles from droppings or nasal secretions of infected birds Sometimes infection is acquired by bite of an infected bird Whereas classic psittacosis is associated with an appreciable mortality rate mortality following infection by related ornithotic strains is lower Spread from man to man has been reported about 30 times

The causative virus belongs to a group of organisms intermediate in morphology and metabolism between true viruses on the one hand and bacteria and rickettsia on the other They resemble bacteria in being susceptible to sulfonamides and penicillin Whereas complement fixing

(9) Am J M S 216 551 564 November 1948.

antibodies result from infection cross reactions make it impossible to differentiate members of the group Differentiation is possible solely through consideration of source of virus and by transmission of disease to animals

Headache photophobia sweating malaise anorexia and abdominal distention resemble those of any infection particularly influenza Bradycardia is characteristic Usually fever is continuous for three or four weeks and defervescence occurs by lysis in patients who recover spontaneously As in other types of virus pneumonia x ray findings are much more pronounced than physical symptoms or signs referable to the respiratory tract Usually x ray findings themselves are minimal however there was no correlation among Wolins cases between clinical severity of illness and degree of pulmonary involvement revealed by x ray

Diagnosis depends on history of contact with birds extensive pneumonitis without dyspnea or much cough and bradycardia in addition to results of laboratory procedures especially mouse inoculation and complement fixation test

Original estimate of mortality was 30-40 per cent but accumulating knowledge suggests that it is closer to 10 per cent Both sulfadiazine and penicillin inhibit growth of viruses of this group In human beings sulfadiazine has been disappointing but penicillin is effective Four of six patients given penicillin in 400 000 unit daily doses responded quickly The drug need not be continued after defervescence

[It is advocated that we discard the term ornithosis and call all of these infections psittacosis It should be realized that infection can be acquired from many birds as well as from parrots —Ed]

Human Psittacosis Cured by Penicillin Therapy is reported by Alfred F Coggio[1] (Berkeley Calif)

Woman 27 was hospitalized for chills fever nausea and flatulence of five days duration Physical examination revealed no abnormalities except a few crepitant rales at the left lung base and moderate abdominal distention Tempera

(1) C l f M d 70 167 1 0 M rch 1949

ture was 105 4 F and white cell count 9 800 Chest x ray revealed infiltration of the left lower lung

Because the patient had had two canaries for the previous 2½ weeks psittacosis was suspected and penicillin administered in doses of 100 000 units every three hours When she failed to respond to treatment the dose was raised to 200 000 units every three hours on the second hospital day and thereafter improvement was rapid By the fifth hospital day temperature was normal and remained so

On the sixth day a report was received of growth of psittacosis virus in both mice and cotton rats inoculated with the patient s sputum a significant complement fixation titer for psittacosis was present in the blood

It is of interest that the virus was isolated from sputum obtained after 24 hours treatment with penicillin Dosage required in this case was higher than that previously reported necessary

[Psittacosis is susceptible to penicillin therapy the dose should be large Even better results may be forthcoming with aureomycin or chloromycetin ®—Ed]

Q FEVER

Q Fever Present Status in the United States is summarized by Elias Strauss and S Edward Sulkin[2] (Southwestern Med College) Q fever gets its name from Queensland Australia where it was first described as an influenza like disease among slaughter house workers *Smears of organs of guinea pigs inoculated with* blood from patients with the disease contained intracellular rickettsial bodies In 1940 Q fever occurred in 16 workers in the laboratory of the National Institute of Health For the first time pneumonia was recognized as a prominent feature of the disease Atypical pneumonia from Q fever was detected in troops in the Mediterranean area during World War II In 1946 an epidemic occurred among packing house workers in Texas and in Chicago and in 1947 over 100 cases were detected in the Los Angeles area

( ) Te a St te Jr Med 44 14 217 July 1948

Q fever is characterized by headache which may be severe and may be associated with photophobia fever and pneumonia demonstrable by x ray Many mild cases probably are not accompanied by pneumonia Despite prominence of pneumonia respiratory symptoms are rare Sore throat nasal obstruction and sneezing are unusual Cough usually occurs but is not often productive Physical signs in the chest are usually normal in the early stages Later rales may be heard but evidence of consolidation is not to be expected Rash splenomegaly and lymphadenopathy do not occur Fever is usually above 102 F and persists for 5 14 days Only five fatalities have been reported Most patients recover without sequelae

White blood cell and differential counts are usually normal Sputum and urinalysis are normal

Pulmonary infiltration seen on x ray is easily differentiated from tuberculosis or bacterial pneumonia but is easily confused with atypical pneumonia Psittacosis and coccidioidomycosis can be eliminated if the patient has had no contact with psittacine birds and has not been in the Southwest Cold agglutinins develop in 25 50 per cent of patients who have had virus pneumonia but do not develop in patients who have had Q fever In virus pneumonia the infiltration is usually feathery and mottled and spreads fanwise from the hilus to the periphery whereas in Q fever infiltrations are often circumscribed of uniform ground glass density and in peripheral portions of the lungs

Diagnosis of Q fever is established by isolating rickettsias from the blood during the acute illness or by demonstrating a rise of titer of specific antibodies during convalescence Isolation of the organism is hazardous and should be undertaken only in special laboratories Agglutination tests for Q fever do not cross agglutinate with other rickettsial diseases

In Australia Q fever is known to be transmitted by ticks but no insect vector has been demonstrated in

ture was 103 4 F and white cell count 9 800 Chest x ray revealed infiltration of the left lower lung

Because the patient had had two canaries for the previous 2½ weeks psittacosis was suspected and penicillin administered in doses of 100 000 units every three hours When she failed to respond to treatment the dose was raised to 200 000 units every three hours on the second hospital day and thereafter improvement was rapid By the fifth hospital day temperature was normal and remained so

On the sixth day a report was received of growth of psittacosis virus in both mice and cotton rats inoculated with the patient s sputum a significant complement fixation titer for psittacosis was present in the blood

It is of interest that the virus was isolated from sputum obtained after 24 hours treatment with penicillin Dosage required in this case was higher than that previously reported necessary

[Psittacosis is susceptible to penicillin therapy the dose should be large Even better results may be forthcoming with aureomycin or chloromycetin *—Ed]

Q FEVER

Q Fever Present Status in the United States is summarized by Elias Strauss and S Edward Sulkin[2] (Southwestern Med College) Q fever gets its name from Queensland Australia where it was first described as an influenza like disease among slaughter house workers Smears of organs of guinea pigs inoculated with blood from patients with the disease contained intracellular rickettsial bodies In 1940 Q fever occurred in 16 workers in the laboratory of the National Institute of Health For the first time pneumonia was recognized as a prominent feature of the disease Atypical pneumonia from Q fever was detected in troops in the Mediterranean area during World War II In 1946 an epidemic occurred among packing house workers in Texas and in Chicago and in 1947 over 100 cases were detected in the Los Angeles area

(2) Texas State J Med 44 214 21 July 1948

ical pneumonia occurring in persons living or working in or near dairies and other collections of cattle in states where positive reactions were found in cattle

[We must have been failing to recognize this disease in the United States since good evidence now indicates that the infection is widely disseminated in this country —Ed]

Q Fever Report of Case in Pennsylvania O Henry Janton Amedeo Bondi Jr and M Michael Sigel[4] (Philadelphia) present a serologically proved case of Q fever thought to be the first report of Q fever naturally acquired in Pennsylvania

Man 36 was hospitalized after sudden onset of chills and fever the previous evening Generalized weakness and aching and a severe persistent headache had developed the day of admission He had a slight cough productive only of white phlegm There was no history of hemoptysis chronic cough dyspnea night sweats and weight loss He appeared acutely ill face was red and flushed skin hot and dry and temperature 103 2 F Nasal mucosa and throat were injected and postnasal discharge was noted Examination of the lungs failed to demonstrate consolidation rales or other abnormalities

Penicillin 30 000 units every three hours was started Next day headache became worse and he complained of sore throat profuse sweating and increased cough Chest x rays showed some accentuation of bronchovascular shadows throughout the mesial aspect of both lung field Penicillin dosage was increased to 50 000 units every three hours He remained acutely ill for the next two days then began to improve and was discharged well eight days after admission

Laboratory studies revealed 5 000 white cells with 80 per cent polymorphonuclears and 20 per cent lymphocytes urinalysis bacteriologic studies of throat spinal fluid study stool examination *blood urea nitrogen blood sugar and agglutination* tests with typhoid O and H paratyphoid A and B Proteus OX 19 and Brucella abortus were all negative Complement fixation tests with antigens of influenza virus type A and B with antigen of the psittacosis lymphogranuloma group of agents and antigen of Q fever rickettsia (American strain) and the cold agglutination test revealed that the patient had antibodies against the rickettsia of Q fever and not against the pneumotropic viruses Finding of an increasing titer of antibodies to Q fever rickettsia established the diagnosis

(4) A I t Med 30 180 184 J y 1949

the United States Occurrence among packing house employees suggests importance of cattle in transmission of the disease but the method of transmission is an enigma

Q Fever Serologic Survey of Bovine Serums in United States Information concerning geographic distribution of Q fever in the United States is incomplete. Reported human cases of naturally occurring Q fever acquired in the United States are confined to two isolated cases in Montana an outbreak in a stockyard and a slaughter house in Amarillo Tex an outbreak among packing house workers in Chicago and the Q fever in Los Angeles County which is apparently endemic The observation in Los Angeles County that about 15 per cent of dairy cows tested showed positive complement fixations for Rickettsia burneti suggested to Charles C Shepard[3] (U S Pub Health Service) another means for investigating geographic distribution of the disease With co operation of the Department of Agriculture five samples of bovine blood serums were collected during the brucellosis testing program from each of 10 herds in 37 states Serums were tested for R burneti antibodies using the Bengtson complement fixation test In all 1,789 serums were tested

Number of serums positive for Q fever in a given state varied from 6 per cent to none Positive serums were found in cattle from 16 states Wisconsin Minnesota Missouri North Dakota Nebraska Virginia Mississippi Texas New Mexico Arizona Kansas Kentucky Colorado Washington Oregon and Pennsylvania Although geographic distribution of positive reactions was spotty all but two of the serums positive for Q fever originated in the Western two thirds of the country These results suggest that human cases of Q fever should be sought especially in parts of the country from which cases have not been reported It would appear advantageous to give attention to cases of atyp-

(3) Am. J Trop Med. 28 849 855 November 1948

hacking cough and mild pleuritic chest pain Onset was characteristically sudden and without prodromal symptoms All patients complained of fever True rigor occurred in only 12 but almost all patients noted chilly sensations early in the illness Severe and persistent headache was a common complaint and usually did not respond to aspirin Symptoms of upper re piratory infection were singularly lacking though most patients complained of mild nonproductive cough Slightly over one third of patients complained of chest pain Anorexia was almost universal and nausea and vomiting were not infrequent

Fever on hospital admission averaged 102 8 F in the 80 cases Average maximum temperature during hospitalization was 103 9 F Fever of 100 104 F was usually sustained an average of 10 days Average pulse rate on admission was 97/minute somewhat lower than would be expected for the average initial temperature of 102 8 F This relative bradycardia was noticeable in most patients Forty seven had pulmonary rales on admission Clinical evidence of meningeal irritation was noted in one fourth of patients and was often severe

Some white cell counts showed leukopenia others leukocytosis the tendency was to mild polymorphonuclear leukocytosis and lymphocytopenia Lumbar punctures were performed on 21 patients during the acute phase of illness all cell counts were normal Cold agglutinins in a titer of 1 32 and of 1 8 were present in 2 cases but were absent in 20

Penicillin was given 61 patients but clinical course of the disease was unaltered Para aminobenzoic acid given three failed to alter the course as did streptomycin given eight Sulfonamides with or without penicillin were also ineffective Aureomycin which appears to be the most effective therapeutic agent in treatment of Q fever was not available

[Note that history of exposure to cattle raw milk or fertilizer c uld be obta ned in only 70 per ce t of the case —Ed]

Significant clinical features were the explosive onset with chills severe and persistent headache marked upper respiratory manifestations with minimal clinical and no x ray evidence of lung involvement febrile course which fell by lysis and was unaffected by penicillin and normal white cell count The fact that these findings initially suggested diagnosis of atypical pneumonia or influenza illustrates need for laboratory aid in differentiating the *etiologic entities grouped clinically under* the heading influenza grippe and atypical pneumonia The authors re emphasize the importance of considering Q fever in diagnosis of nonbacterial pneumonia

The mode of infection of this patient was not clearly established He worked in a dusty atmosphere in a wool processing factory Other cases of Q fever were subsequently recognized there It seemed probable that the *infecting agent* was carried *in* the wool and that the respiratory tract was the portal of entry

Clinical Aspects of Q Fever in Southern California Study of 80 Hospitalized Cases Of the first 250 patients with proved Q fever in Southern California 110 were hospitalized in different hospitals Ross B Denlinger[5] (Long Beach Calif) selected the records of 80 for study

History of possible exposure to potentially infectious material could be elicited from only 70 per cent Any contact with unpasteurized milk handling of fertilizer or even residence within several blocks of a dairy were considered grounds for classification as exposed personnel Only a few reported close contact with cattle or their products but some type of possible exposure could be discovered by detailed questioning in all but 30 per cent

Patients presented no distinctive or pathognomonic symptoms the *usual symptom complex being sudden* onset of fever chilly sensations malaise anorexia and severe headache followed in a few days by a slight

(5) A I t M d 30 510 527 M h 1949

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[Note th t history of exposu e to cattle raw milk or fertilizer could be obtained in only 70 per cent of the cases —Ed]

Treatment of Q Fever in Man with Aureomycin E H Lennette G Meiklejohn and H M Thelen[6] (San Francisco) present data on 14 patients with Q fever who were treated early in the disease and on whom etiologic studies confirming the clinical diagnosis have been completed Since this disease tends to run a longer course and be more severe in older persons most of the patients selected for treatment were over 30 All but one had been ill for four or more days and all were becoming increasingly ill when therapy was started Most patients had temperatures (oral) of 104 F or more

The first four patients were given 40 mg aureomycin hydrochloride daily intramuscularly As results were not satisfactory the other 10 patients were given aureomycin orally From 3 2 to 4 Gm was administered in the first 24 hours then 1 6 or 2 Gm daily for four or more days Total dose ranged from 8 to 27 5 Gm In every instance symptomatic improvement manifested best by return of appetite was noted within 48 hours after therapy was begun and a considerable decline of temperature occurred within 48 72 hours Temperatures of eight patients fell to normal during the first three days of therapy and those of the other two became normal in four or five days Use of the drug was discontinued in some patients within 24 hours after temperature became normal Relapses occurred in two patients after cessation of therapy but subsided promptly after reinstitution of aureomycin

Mild symptoms referable to the gastrointestinal tract occurred during therapy in four patients but all of them had had similar complaints before therapy was instituted

Since the febrile period was considerably shorter in the patients treated with aureomycin than in patients of a similar age group not so treated it is concluded that oral aureomycin therapy offers promise in treatment of Q fever and that further investigations are desirable to evaluate usefulness of this drug

(6) Ann. New Y k Acad Sc 51 331 342 No 30 1948

VIRAL HEPATITIS

Methods of Protection against Homologous Serum Hepatitis—*Inactivation of Hepatitis Virus SH with Ultraviolet Rays*—Experiments done by Mercer C Blanchard Joseph Stokes Jr Bettylee Hampil George R Wade and John Spizizen[7] (Univ of Pennsylvania) indicate that the virus producing serum hepatitis is de stroyed by ultraviolet irradiation of plasma Irradiation may be accomplished by use of the Oppenheimer Levinson or the Habel Sockrider apparatus both of which irradiate continuously flowing thin films of plasma Previous work has shown that such irradiation does not significantly alter plasma proteins

In the present studies a Habel Sockrider apparatus was used This consists of a rotating glass tube 52 cm long and 2 53 cm in diameter with an 18 watt cold quartz lamp passing lengthwise through the center of the tube The lamp has an intensity of 3 500 microwatts/sq cm at the distance used About 85 per cent of its radiation is in the 2 537 A wavelength The glass tube was rotated 240 times a minute at an angle of 12 degrees from the horizontal The film of serum was 0 263 mm thick and time of exposure 10 seconds

Of 15 volunteers given nonirradiated icterogenic serum hepatitis developed in 7 whereas of 11 volunteers given irradiated icterogenic serum none showed evidence of hepatitis

Electrophoretic studies and chemical fractionation failed to reveal evidence of alteration of electrophoretic pattern in similarly irradiated plasma but a slight de crease in prothrombin and complement was detected Like neurotropic viruses the virus of serum hepatitis is unusually resistant to physical and chemical agents For this reason it was found necessary to irradiate plasma

(7) J A M A 138 341 343 Oct 2 1948

for 10 seconds With the method used the earliest detectable protein changes are after plasma has been run through the machine at a rate of 16 cc a minute Rate of flow in this study was 24 cc a minute

Inoculation of 11 volunteers with irradiated serum produced no allergic reactions

[Ultraviolet radiation will not inactivate this virus in whole blood and we continue to encounter occasional cases of serum hepatitis in patients who have received blood transfusions two to four months previously Protection with two injections of gamma globulin (see next article) at 30 day intervals is not generally practicable in civilian hospitals —Ed]

Studies on Protective Value of Gamma Globulin in Homologous Serum Hepatitis SH Virus —Joseph Stokes Jr Mercer Blanchard John R Neefe Sydney S Gellis and George R Wade[8] (Univ of Pennsylvania) point out that certain characteristics differentiate serum hepatitis from infectious hepatitis Clinically the two may often be differentiated by their different incubation periods 60 150 days for serum hepatitis and 18 40 days for infectious hepatitis

Gamma globulin obtained by fractionation of blood from large Red Cross pools has been administered to patients exposed to each of these two types of hepatitis in the hope that it might contain sufficient antibodies to prevent or attenuate the two diseases Studies in several epidemics demonstrated the ability of such gamma globulin to prevent infectious hepatitis Given in doses of 0 06 0 15 cc /lb body weight gamma globulin protected a large proportion of exposed susceptible persons

Studies of the effect of gamma globulin on serum hepatitis were conducted in two widely separated army general hospitals on men given blood or pla ma at the time of injury Gamma globulin was given alternate patients in each hospital In one hospital two doses of 10 cc each were given 30 days apart Excellent protection appeared to have been afforded in these patients In the second hospital a single 10 cc dose was given No pro

(8) J A M A 138 336 341 O t 2 1948

tection resulted but the incubation period of the disease was prolonged more than 50 per cent a phenomenon not observed when gamma globulin was given patients during the incubation period of infectious hepatitis

As a result of this study all army general hospitals were directed to administer routinely on admission a single intramuscular injection of gamma globulin to all patients hospitalized because of battle injuries and given transfusions at time of injury Since this order made further controlled studies of large groups impossible the authors undertook studies of small groups of volunteers

In these studies however the gamma globulin tested apparently did not contain virus neutralizing or inhibiting factors effective against the strain of serum hepatitis virus used In a single small study hepatitis convalescent plasma from one subject failed to provide inhibiting factors against the same strain of serum hepatitis virus

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NEUROTROPIC VIRUS DISEASES

Meningoencephalitis in Man Due to Louping Ill Virus is reported by George Davison Charles Neubauer and E Weston Hurst [9] Louping ill has been well known in certain areas of Scotland and the border counties of England for over a century and has been studied extensively because of its high mortality among sheep Infection is conveyed from sheep to sheep by the tick Ixodes ricinus Six cases have been reported in human beings all laboratory workers The two cases presented here are the first in which infection is assumed to have been acquired naturally

CASE 1—Man 47 had a slight chill after working for a week at sheep dipping Some of the heep had been infested with I ricinus and he had brushed several ticks from his arms After six days of malaise his physician found only a high temperature and slow pulse Fever persisted for five days then

(9) La t 2 453 457 S pt 18 1948

for 10 seconds With the method used the earliest detectable protein changes are after plasma has been run through the machine at a rate of 16 cc a minute Rate of flow in this study was 24 cc a minute

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(8) J A M A 138 336 341 Oct 2 1948

During the first four weeks of illness the first patient had been in contact with four patients who shared her room several other patients who visited her regularly and several nurses Two nurses became ill 13 and 19 days after the first patient began to show symptoms Then other nurses and patients among her contacts became ill but they could have been infected by the second and third patients The three subsequent cases were due to contact with the second patient after 11 16 and 17 days The remaining cases followed at intervals of one to five days The numerous mutual contacts in the various rooms made infection possible from all directions An average incubation period of 11 19 days could be inferred from the first six cases There were two cases in which contact with other patients ill with the disease or in the incubation period could not be demonstrated they had naturally been in contact with nurses who attended encephalitis patients and some of the nurses may have been healthy virus carriers

Since virus was present in patients nasopharynx aerogenous route of infection was the most probable It was impossible to trace the source of the infection From some patients cerebrospinal fluid blood and throat a virus was isolated that at first caused choriomeningitis in guinea pigs only but after passage through guinea pigs infected mice This virus as well as two strains of choriomeningitis virus were not or only slightly neutralized by serum of patients in the acute phase but were strongly neutralized by the serum of convalescent patients St Louis and equine encephalomyelitis viruses were not neutralized by these serums There was complete cross immunity between the choriomeningitis virus and the causal agent of the epidemic

subsided spontaneously Five days later he had a relapse characterized by headache and vomiting Because these symptoms persisted he was hospitalized Physical examination revealed little of significance except mental confusion Spinal fluid was clear and under 180 mm pressure it contained 0 04 Gm protein/100 ml and 17 lymphocytes/cu mm

Fever responded to neither penicillin nor sulfadiazine but subsided spontaneously on the sixth hospital day Clinical symptoms then subsided

CASE 2—Farmer 59 was hospitalized with a provisional diagnosis of meningitis For several months he had had malaise anorexia and weight loss Headache and stiffness of the neck developed four days before hospitalization Examination revealed marked neck stiffness but no Kernig sign Though fully conscious he appeared to be deaf and confused His condition deteriorated and two days after admission he was stuporous and incontinent The fifth day fever ended by crisis and thereafter clinical condition improved gradually He was hospitalized for 10 weeks and on discharge was well except for a somewhat stooped gait failure to swing the right arm during walking and an extensor plantar response on the right

Blood was collected from the first patient 55 days after onset of symptoms and from the second patient at 9 and 23 days Serum was mixed with varying dilutions of louping ill virus of known titer and then inoculated intracerebrally or intramuscularly into six mice As controls similar dilutions of virus were mixed with normal serum and injected into mice Definite neutralization of the virus was demonstrated in both patients

Louping ill should be considered whenever meningoencephalitis appears in a person exposed to sheep

Encephalitis Epidemic Caused by Infectious Agent Closely Related to Armstrong's Choriomeningitis Virus During the winter of 1946-47 J D Verlinde J van der Werff and W Briet Jr[1] (Leiden) observed 25 cases of subacute benign encephalitis without residuals in a convalescents home which then sheltered 46 women 29 men and 7 children under 10 and employed 14 nurses and 12 servant girls All but one of the cases occurred in women 13 patients 8 nurses and 3 servants

(1) Nederl tijdschr v geneesk 9 30 809 Sept 11 1948

by 46 men in some 25 30 lb Many noted disappearance of persistent headaches which previously had not re sponded to any therapy Practically all commented on their improved feeling of well being

[These results are splendid considering that all the patients had chronic relapsing malaria —Ed]

COLLAGEN DISEASES

Studies on Rheumatic Fever Observations on Tonsil lar Carriers of Hemolytic Streptococci Effect of Tonsil lectomy and Administration of Penicillin on Rheumatic and Nonrheumatic Fever Patients is reported by Harold G Nelson[3] and personnel of U S Naval Medical Research Unit 4 (U S Naval Hosp Dublin Ga) This study was conducted in a hospital devoted primarily to care of patients convalescing from acute rheumatic fever Cul tures were made from throats and later from tonsils removed from 75 patients with rheumatic fever and 64 patients who did not have rheumatic fever

Pathogenic streptococci were recovered from tonsils of 33 3 per cent of patients with rheumatic fever and from 15 6 per cent nonrheumatic fever patients Throat cultures before tonsillectomy revealed pathogenic strep tococci in 2 7 per cent of rheumatic fever patients and 3 1 per cent of nonrheumatic fever patients The greater incidence of positive cultures obtained from tonsils than from the throat in rheumatic fever patients suggests that patients continue to harbor streptococci in the ton sils long after acute attacks of rheumatic fever

When patients with rheumatic fever of continued activity were considered separately from those in whom the disea e had become quiescent no difference in inci dence of positive throat cultures was found

There was no clinical or laboratory evidence that tonsillectomy combined with postoperative penicillin

(3) J I f ct D 83 138 146 S pt O t 1948

Cure of Chronic Vivax Malaria with Pentaquine is reported by L T Coggeshall and Fred A Rice[2] (Univ of Chicago) Although quinine and quinacrine hydrochloride promptly relieve acute malaria relapses are common when these drugs are used Many new drugs were discovered in an intensive research program conducted by the National Research Council during World War II This report concern one of these pentaquine a derivative of pamaquine naphthoate (plasmochin®) Pentaquine is more effective and less toxic when used to treat Plasmodium vivax than is plasmochin® Pentaquine was more effective if quinine was given simultaneously In this study it was given 185 men who had contracted vivax malaria in the Pacific Orient Mediterranean and West Indies and still had positive blood smears Number of relapses before treatment varied from 1 to 50 One 30 mg pentaquine tablet was given three times daily with 2 tablets of quinine sulfate each containing 1 Gm three times daily Both were administered 14 days Later in the study 1 Gm quinine three times daily was found sufficient and resulted in less cinchonism

Only 4 of the 185 refused to complete therapy supposedly because of gastrointestinal upset Toxicity occurred in 43 subjects and consisted of tinnitus dizziness abdominal cramps and deafness Among the 185 there were 10 verified failures with positive blood smears and 10 with chills and negative blood smears There were no further objective findings referable to malaria after treatment in 163 most of whom were followed six months or longer Patients and physicians were enthusiastic about the striking relief from symptoms associated with malaria Immediate significant gain in weight was noted

(2) J A M A 139 43 439 Feb 1 1949

by 46 men in some 25 30 lb Many noted disappearance of persistent headaches which previously had not responded to any therapy Practically all commented on their improved feeling of well being

[These results are splendid considering that all the patients had chronic relapsing malaria —Ed]

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When patients with rheumatic fever of continued activity were considered separately from those in whom the disease had become quiescent no difference in incidence of positive throat cultures was found

There was no clinical or laboratory evidence that tonsillectomy combined with postoperative penicillin

[3] J I f t D 83 133 146 S pt O t 1948

therapy had an adverse effect on patients who exhibited low grade rheumatic activity immediately before or at the time of tonsillectomy

It was concluded that routine throat cultures do not provide an accurate index of the carrier rate of hemolytic streptococci and that cultures of excised tonsils give more accurate data on actual incidence of streptococcus carriers

Orally Administered Penicillin in Patients with Rheumatic Fever Benedict F Massell James W Dow and T Duckett Jones[4] administered penicillin orally to all patients at the House of the Good Samaritan *Boston* with hemolytic streptococci in throat cultures from July 1946 through June 1947 Purpose of the study was to determine if orally or intramuscularly administered penicillin would reduce hemolytic streptococcus carrier rate in ward patients if such reduction in carrier rate plus prompt penicillin therapy of patients acquiring streptococcus infections would reduce spread of infection among ward patients if hemolytic streptococci could be eradicated from patients throats by infrequent oral doses of penicillin and if prompt treatment of hemolytic streptococcic infection would influence immune response and prevent rheumatic fever recurrences

Penicillin was given by mouth as 50 000 100 000 unit buffered tablets at least one hour before meals and two to four hours after meals No food was allowed between meals Orally administered penicillin in doses of 300 000 1 000 000 units daily for 10 days suppressed hemolytic streptococci in throats of all but 2 1 per cent of patients with rheumatic fever during therapy and eradicated organisms in *77 7 per cent* This reduction of streptococcus carrier rate by penicillin even with prompt treatment of hemolytic streptococcus infections with penicillin did not however completely prevent spread of streptococcus infections among ward patients Suppression of hemolytic streptococci in the throat by doses of 100 000

(4) J A M A 138 1030 1036 Dec 4 1948

200 000 units of penicillin as infrequently as three times a day suggested that similar dosages might be practicable for prevention of hemolytic streptococcus infections and hence of rheumatic fever

Of 10 patients with clinical and 5 with subclinical hemolytic streptococcus infections and rheumatic fever who were promptly treated with penicillin none had recurrence of rheumatic fever The authors are loathe to conclude that penicillin prevented rheumatic fever recurrences because occasional hemolytic streptococcic strains are unable to produce rheumatic fever However they regard the evidence as suggestive

[The cautious interpretation of results described in the l t paragraph is to be applauded the point is of course of the greatest importance —Ed]

Rheumatic Infection in Childhood 15 20 Year Follow Up, Caution against Early Ambulant Therapy Rachel Ash[5] (Univ of Pennsylvania) presents results of a follow up study of 331 rheumatic children 15 years after onset of infection and of 150 children 20 years after onset (see table) Incidence of carditis and of deaths within the first 10 years was greater among those taken ill during 1923 27 than during 1928 32 and least among those taken ill during 1933 37 Part though not all of this improvement may be due to a spontaneous change in the character of the disease Shift in racial composition of the group observed could not explain the decreased mortality and lessened carditis since the number of Negro children increased and such a change should have worsened the situation since death rate has been higher among Negro than among white children Decline in incidence of carditis cannot be ascribed to variation in method of using salicylates Throughout the study period it was customary to administer large doses of salicylates at the beginning of the disease but not to continue the drug in the absence of fever and joint pain About 1928 use of adequate doses of digitalis in treatment of heart failure associated with acute rheumatic carditis was

(5) Am J D Ch ld 7 465 J ly 1948

begun Probably a few children were pulled over a critical period by use of this drug The drug was most useful in treatment of children in whom dyspnea was the predominant manifestation of heart failure and of much less value in those with predominant signs of right heart failure marked enlargement of the liver and edema

Major change in treatment during the study period was in duration of hospital stay or bed rest at home Whereas in the early part of this period most children were returned home shortly after disappearance of acute

OUTCOME OF RHEUMATIC INFECTION IN CHILDREN OBSERVED FOR 20 YEARS AFTER ONSET

No Traced	Total	Rheumatic Heart Disease No	%	Deaths: Rheumatism No	%	S.B.E.* No	Other Causes No	Dead to [illegible]
176	95 6	118	67 1	22	12 5	0	0	1
175	95 1	125	71 4	43	24 6	2	2	5
173	94 0	118	68 2	60	34 7	4	3	10
163	83 1	116	71 1	68	41 7	6	4	15
150	81 5	114	76 0	73	48 7	6	4	20

* Subacute endocarditis

symptoms children are now hospitalized an average of three months after which they are discharged to a convalescent home or sent home under supervision of the Visiting Nurse Society and the Rheumatism Clinic until all signs of active infection have disappeared Bed rest in the presence of active rheumatic infection is recommended regardless of the presence or absence of clinically recognizable heart disease

Whether the lessening of severity of the disease during this period is partly due to the favorable influence of prolonged bed rest at onset of infection or entirely due to a spontaneous change in character of the disease is a matter of speculation but it would seem wise for physicians to give prolonged rest in bed the benefit of the doubt and not be tempted to institute early ambulant treatment in care of the rheumatic child

Pediatricians seem convinced that prolonged bed rest after acute

rheumatic fever is desirable Those whose experience is principally with adults are not so uniformly in agreement on the point—Ed]

Does Sodium Salicylate Cure Rheumatic Fever? In an attempt to answer this question James Reid[6] (Univ of Glasgow) studied 9 adults and 3 children with rheumatic fever Seven of the adults were given 2 Gm sodium salicylate and 2 Gm sodium bicarbonate five times a day the other two received 2 Gm sodium salicylate alone five times daily Two of the children were given 1 3 Gm sodium salicylate and 1 3 Gm sodium bicarbonate and the third child received 1 3 Gm sodium salicylate alone five times daily All medication was given orally

The lowest salicylate levels for the entire group during the first three weeks of treatment ranged from 11 to 31 mg /100 cc for plasma and 183 to 257 mg for urine In the seven adults receiving bicarbonate salicylate levels reached a peak in three to eight days ranging from 20 to 46 mg /100 cc for plasma and 303 to 588 mg for urine In all patients but especially in children both plasma and urinary salicylate levels tended to fall after the initial peak levels were reached despite continuous drug administration The fall was associated with changes in acid base balance a rise in plasma and urinary salicylate was associated with acidosis and a fall with changes in the opposite direction Bicarbonate administration tended to depress plasma salicylate levels by increasing urinary salicylate excretion Disappearance of joint pains fever and tachycardia was related to plasma salicylate concentration Relapses coincided with a sharp fall in plasma salicylate levels and remissions with a rise in plasma levels

Erythrocyte sedimentation rates before treatment ranged from 95 to 122 mm in one hour and after three weeks they were either approaching or had returned to normal in all but one patient When average plasma salicylate level was less than 20 mg /100 cc sedimentation rate showed no sign of falling when the level was

(6) Q J Med 17 139 151 Ap 1948

20-30 mg the rate fell slowly and when it was 30-40 mg the rate rapidly returned to normal In one patient with average plasma salicylate level of 17 mg./100 cc sedimentation rate was unchanged during the first three weeks of treatment When average salicylate level was increased to 27 mg by doubling the dose of sodium salicylate and sodium bicarbonate sedimentation rate rapidly returned to normal It is therefore concluded that if erythrocyte sedimentation rate is a reliable index of rheumatic activity sodium salicylate has a curative action directly related to plasma concentration of the drug It appears desirable to keep plasma salicylate levels between 30 and 40 mg./100 cc while the disease is active

[Reid s observation that the blood salicylate level tends to decline after the first few days on a given dosage could be correlated with clinical experience that fever and joint pain sometimes tend to reappear while therapy is being continued Because of unpleasant side effects it is difficult to maintain the plasma salicylate level between 30 and 40 mg./100 cc in all patients—Ed]

Treatment of Acute Rheumatic Fever with Aspirin with Special Reference to Biochemical Changes William S Hoffman Mark Pomeranc Italo F Volini and Catherine Nobe[7] (Hektoen Inst Chicago) treated 80 adults with acute rheumatic fever with aspirin until disappearance of clinical symptoms of the disease The product used was alasil® tablets of which contain 4 gr aspirin 2 gr colloidal aluminum hydroxide and an excipient Control tablets were of the same size and contained 4 gr aspirin but 2 gr starch instead of aluminum hydroxide

Of 65 patients started with control tablets 8 complained of gastric distress Distress disappeared when tablets containing aspirin and aluminum hydroxide were substituted For most of the therapy period therefore aspirin plus aluminum hydroxide was administered to all patients

With 4-6 tablets every four hours fever pain and

(7) Am J Med 6 433 442 Apr 1 1949

tenderness in involved joints were usually relieved in 24-48 hours even before plasma salicylate concentration had risen to levels of 30 mg/100 cc or more Such concentrations were usually achieved by the third day Once the desired plasma level had been reached it could be maintained by giving 4-6 tablets every six hours instead of every four

Almost all patients in whom levels of 30-40 mg/100 cc were maintained for several days showed one or more symptoms of salicylism Only 41 patients could be maintained at an average plasma salicylate level above 25 mg/100 cc The other 39 had to be given doses that produced levels under 25 mg/100 cc Comparison of the effect of high and low plasma salicylate concentrations on sedimentation rate showed only a slight superiority of the high levels in reducing sedimentation rate to normal by the time clinical symptoms had completely disappeared

Prothrombin concentrations were only slightly affected by aspirin therapy The level dropped below 75 per cent of normal in a third of the cases there being no difference in incidence between the high and the moderate dose group In only one instance did prothrombin level fall to a dangerously low level (20 per cent) A moderate fall in serum bicarbonate level occurred in most patients associated with elevated serum chloride value and a slightly diminished serum sodium level Blood pH was usually normal and urine usually acid It is suggested that salicylate produces primary hyperpnea with alkalosis but the accumulated salicylate produces a fixed acid acidosis and that the two effects are mutually compensatory

Study of urinary salicylate clearance revealed that for any given plasma salicylate level salicylate excretion was markedly increased when additional base was made available This suggests that alkalinization is of prime importance in treatment of salicylate poisoning

20 30 mg the rate fell slowly and when it was 30 40 mg the rate rapidly returned to normal In one patient with average plasma salicylate level of 17 mg /100 cc, sedimentation rate was unchanged during the first three weeks of treatment When average salicylate level was increased to 27 mg by doubling the dose of sodium salicylate and sodium bicarbonate sedimentation rate rapidly returned to normal It is therefore concluded that if erythrocyte sedimentation rate is a reliable index of rheumatic activity sodium salicylate has a curative action directly related to plasma concentration of the drug It appears desirable to keep plasma salicylate levels between 30 and 40 mg /100 cc while the disease is active

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(7) Am. J M d 6 433 44 Ap 1 1949

eases other than rheumatoid arthritis and to establish further evidence of the histologically specific nature of the polymyositic nodules in rheumatoid arthritis

All muscle specimens were obtained either by biopsy or from amputations and were routinely fixed in formalin* and stained with hematoxylin and eosin Each section was examined first without knowledge of clinical

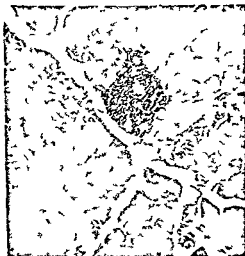


Fig 13—Rh m toid rth t Sk l tal m scl b p y H m to yl d eo d d f m × 150 (Cou te y f St G d Ch J L Am J Cl n P th 18 931 939 D mb 1948)

diagnosis and then after diagnosis was known Material consisted of 126 controls and 27 patients with all stages of rheumatoid arthritis

No special effort was made to remove muscle in the neighborhood of subcutaneous nodules or involved large joints in patients with rheumatoid arthritis Myositic nodules found in 26 of the 27 patients were sharply circumscribed and always located in the endomysium and/or perimysium and rarely in the epimysium These

"Rheumatoid Disease" with Joint and Pulmonary Manifestations Philip Lllman and R E Ball[8] (St Stephen s Hosp London) report three cases

CASE 1 —Man 47 was hospitalized because of an illness of 2½ years duration characterized by pain and stiffness of knees elbows wrists and fingers Breath sounds were dimin ished and there were crepitant rales at both bases Muco purulent cough developed with fever dyspnea and cyanosis These symptoms were unaffected by penicillin and increased in severity until he died six months after admission The lungs were firm throughout with nodular areas suggestive of bron chopneumonia the picture on section suggested chronic fibros ing pneumonitis Histologic tudy revealed interstitial pneu monitis with well marked fibrosis and terminal broncho-pneumonia

CASE 2 —Women 48 was hospitalized because of cough weight loss and arthritis the latter of nine months duration Chest x ray showed bilateral basal opacities and reticular shadows extending into the midzones Fever persisted de spite penicillin The chest x ray picture remained unchanged Attempts to determine the cause of the lung disease were fruit less and the patient died three months after admission Autopsy findings resembled those in Ca e 1

CASE 3 —Woman 55 was hospitalized because of joint pains of three months duration No chest abnormalities were detected until nine months later when cough drew attention to the chest and alteration of breath sounds and rales were found throughout both lung fields X rays at this time showed widespread heavy reticulation and miliary mottling through out the lung fields Bacteriologic examination of sputum re vealed no abnormality Seven months later the patient was alive but the condition was essentially unchanged

Because of the widespread nature of the disease in some patients the authors recommend replacing the term rheumatoid arthritis with rheumatoid disease

[The e cases emphasize the point that rheumatoid arthritis is a systemic disease Occasionally it can hardly be differentiated from dis emmated lupus erythematosus —Ed]

Differential Diagnosis of Rheumatoid Arthritis by Biopsy of Muscle Gabriel Steiner and J L Chason[9] attempted to determine from biopsy material the inci dence of cellular infiltrations in skeletal muscles in dis

(8) P t M J 2 816-8 1 Nov 6 1948
(9) Am J Cl n Path 18 931 939 D c mt 1948

Effect of Hormone of Adrenal Cortex (17-Hydroxy 11 Dehydrocorticosterone Compound E) and of Pituitary Adrenocorticotrophic Hormone on Rheumatoid Arthritis Preliminary Report Philip S Hench Edward C Kendall Charles H Slocumb and Howard F Polley[1] report results of compound E therapy in the first 14 patients so treated all had severe or moderately severe rheumatoid arthritis The authors believed that although the pathologic anatomy of rheumatoid arthritis is more or less irreversible the patholo ic physiology of the disease is potentially reversible sometimes dramatically so Relief of the disease accompanying jaundice or preg nancy made it difficult to believe that rheumatoid arthri tis is caused by bacteria It seemed more likely that the disease was a biochemical disturbance which was tran siently corrected by biologic changes occurring in a number of apparently unrelated conditions With this in mind a search was undertaken to find a biochemical de nominator common to pregnancy jaundice and other conditions known to precipitate improvement in patients with rheumatoid arthritis Many agents were used among which were adrenal hormones

Compound E was given more or less continuously for six months to five patients and for 8 61 days to nine other patients with moderately severe or evere rheu matoid arthritis Symptoms were of 4½ months to 5 years duration Those who had had the disease less than six months were nevertheless severely disabled Without precedent as to dosage the drug was first used in 100 mg amounts daily It has since been found that 25 50 mg doses are inadequate

Usually optimal improvement occurred within the first one or two weeks of treatment and thereafter daily dose was reduced in an attempt to find a smaller effective maintenance dose Usually exacerbations occurred when dose was diminished and it has been concluded that a dose of 75 100 mg daily is required Figure 14

(1) P St ff M t M y Cl n 24 181 197 Ap 13 1949

nodular infiltrations (Fig 13) usually were composed of an inner group of lymphocytes with an outer layer of irregularly disposed plasma cells A small blood vessel was often seen at the periphery and little connective tissue was present in the nodule

In 12 normal controls no cellular infiltration was found in any muscle sections In 18 of 70 patients with atherosclerosis and gangrene cellular accumulations of all types were found Infiltrates were composed either of neutrophils only or of a diffuse mixture of neutrophils and lymphocytes No purely lymphocytic and plasma cell infiltrations were seen Cellular infiltrations were found in 7 of 16 patients with disseminated lupus erythematosus In five of the seven infiltrations were composed of neutrophils and lymphocytes and an occasional plasma cell and were easily distinguished from infiltrations found in rheumatoid arthritis The remaining two lesions more closely resembled those of rheumatoid arthritis and in one of these differentiation could not be made Infiltrations in four patients with thromboangiitis obliterans were composed of neutrophils mononuclear macrophages lymphocytes eosinophils and plasma cells Sections from four patients with dermatomyositis contained poorly demarcated infiltrations composed of lymphocytes and neutrophils with some eosinophils and plasma cells In trichinous infection of skeletal muscle study of multiple sections always revealed the parasite and/or many eosinophils and neutrophils No infiltrations were seen in muscles of four patients with scleroderma Of six patients with miscellaneous diseases of muscles and six with nonrheumatoid polyarthritis four had infiltrations but there was no similarity to those seen in rheumatoid arthritis

The authors conclude that typical nodular cellular infiltrations in skeletal muscles occur in a high percentage of patients in all stages of rheumatoid arthritis Cellular infiltrations sometimes seen in nonrheumatoid diseases can usually be distinguished histologically

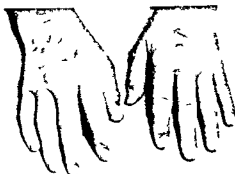
shows metacarpophalangeal joint swelling of one patient before treatment Nine days after beginning use of compound E the swelling had disappeared (Fig 15) but six days after therapy was discontinued it recurred (Fig 16) Sedimentation rate before therapy was 50 mm in one hour after nine days therapy it was 10 mm and six days after discontinuing therapy it was 38 mm

In each of the 14 patients stiffness and aching of joints were strikingly reduced and joint and muscle function was significantly improved within a few days after beginning of therapy Usually stiffness diminished first pain next and finally swelling Appetite often improved rapidly and several patients had marked weight gains Several patients stressed loss of toxicity of the disease and experienced a sense of well being so suggestive of euphoria that psychiatric investigation has been initiated

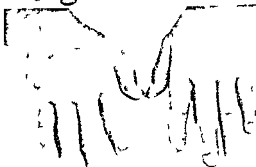
Without the patient s knowledge injection of the hormone was abruptly replaced by injection of a control preparation in nine patients in eight symptoms returned within two to four days In every instance when compound E or its acetate was used sedimentation rates decreased strikingly Usually this decrease occurred within the first few days of therapy and averaged 2-4 mm change a day In most patients sedimentation rates became normal within 10 35 days after treatment was instituted

Pituitary adrenocorticotrophic hormone was given two patients with severe rheumatoid arthritis both of whom showed marked clinical improvement essentially similar to that resulting from use of compound E It is unlikely that compound E will be available for treatment or additional research until sometime in 19 0 the supplies then will be exceedingly small

[This i the most excit ng work of the past year The p esent lack of availability of compound F is ta talizing and no prediction can be made regarding its value in the l ng term management of rheumatoid arthritis Nevertheless the d scovery of th immediate dramat c effect on the d sease should lead eventually to real understand ng and succes ful treatment not only of rheumatoid arthriti but of many related diseases (see next art cle) Hench and Kendall







F 14 (t) —P t e t h ds f ho b fo at t f i j ct f co i po d E te Not w ll or m ta p ph l g l j t o b h h ds se m n n te (W t g en) w s 30 mm h

F 1 (c te) —Ha d of me pat e t d tter b g g ue com d E a t te 300 mg the fi st d a d 100 mg d l j to n th d t l Sw ll g t bl de d m t t n te 10 mm o h

F 16 (b tt m) —H ds t me pat e t s x d aft l j t o f omp d E a et t wa d t j \ t n t w ll g p call o m t c poph l n l j ts t both ha d c d m t t o a th d s lat r w 38 mm i h

(Co t of He ch P S t l P oc t ff M t M yo Cl 24 181 197 Ap 13 1949

on the sixth day in the other Sedimentation rates became *normal* in 12 16 and 18 days in the three patients Tachycardia disappeared after 3½ days in one patient and after 5 days in another in the third tachycardia was not significant Thereafter an unexplained bradycardia occurred in all three and persisted while a dose of 200 *mg* compound E was used but disappeared

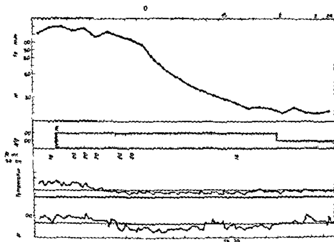


Fig 17 —Eff t of mpou d E a tat t mpe tu p t t d m t t h d P R t n l b y 17 (C t y f H h P S t l P oc St ff M t M y Cl n 24 7 9 M y 5 1949)

shortly after dosage was reduced to *100* mg daily Prolonged P R intervals *in* two patients were restored to normal seven and eight days after treatment was begun In 24 hours after the compound was administered the patients appeared alert instead of ill and toxic and reported an improved sense of well being which has persisted to the time this report was written

During the three to five weeks *the* drug was administered there was no significant change in concentrations of blood urea chlorides sodium potassium or in carbon

and their associates have opened the way to a great advance in medical knowledge —Ed]

Effects of Adrenal Cortical Hormone 17 Hydroxy 11 Dehydrocorticosterone (Compound E) on Acute Phase of Rheumatic Fever Preliminary Report Philip S Hench Charles H Slocumb Arlie R Barnes Harry L Smith Howard F Polley and Edward C Kendall (Mayo Clinic) administered the adrenal cortical hormone 17 hydroxy 11 dehydrocorticosterone to three patients with acute rheumatic fever In each patient fever tachy cardia polyarthritis and abnormalities of sedimentation rate and electrocardiograms all rapidly disappeared Compound E acetate was administered intragluteally as a suspension of finely ground crystals in solution of sodi um chloride in concentration of 25 mg/cc One case follows

Boy 17 was hospitalized because of acute polyarthritis and fever of 12 days duration following a sore throat and cough Sulfonamides and penicillin had had no effect When hos pitalized he was acutely ill with temperature 101 102 F pulse rate 90 100 red pharynx and distinct swelling and pain in the ankles toes and knees Sedimentation rate was 111 mm leukocyte count 13 900/cu mm with 76 per cent poly morphonuclear cells Although no friction rub was heard an electrocardiogram showed abnormalities suggesting acute pericarditis

The next day arthritis progressed to the upper extremities Compound E acetate was given intragluteally in a dose of 100 mg and thereafter in doses of 200 mg daily for 18 days Joint pain diminished five hours after the initial dose Four days later joint pain had almost entirely disappeared and sedimen tation rate had started to decrease The next day temperature and pulse were normal and 10 days after start of treatment the patient felt well and was eating normally Figure 17 shows that sedimentation rate fell progressively from the fifth to the twentieth day of treatment and was at that time normal

After administration of compound E was begun fever which had been present in the three patients 4 11 and 12 days disappeared in 2½ days in one in 4½ days in another and in 1 day in the third Joints were asympto matic on the third day of treatment in two patients and

(2) P oc St ff Meet M yo Cl 24 277 297 M v 25 1949

sodium 0 1 Gm three times daily and had taken the drug continuously Two months before admission loss of appetite and dull pain in the upper abdomen developed and he passed black stool and vomited small amounts of blood These symptoms subsided however Three weeks before admission a diffuse maculopapular rash injection of scleras and spots on the oral mucosa appeared Ulcerative stomatitis developed 10 days later

On admission the patient appeared considerably dehydrated The skin was moderately edematous and small flakes were desquamating over the entire body Large sheets of skin were peeling from palms and soles Hard shotty discrete nodes were present in the left cervical area and inguinal regions Scleras and conjunctivas were injected and the oral mucosa was covered by confluent indurated necrotizing ulcers The chest was emphysematous and breath sounds were harsh and bronchial with inspiratory and expiratory rhonchi Peripheral arteries were thickened and tortuous Routine laboratory and x ray studies revealed no abnormalities except moderate anemia Despite intramuscular injection of penicillin local treatment of the eyes and mouth and supportive therapy he died nine days later At autopsy inflammatory necrotizing arterial lesions of the type occurring in serum sickness and in hypersensitive reactions to sulfonamides and to iodine were present in the liver spleen kidneys bone marrow and skin

Continued medication with dilantin® sodium and certain other drugs after clinical evidence of hypersensitivity has developed is fraught with danger since the clinical picture of periarteritis nodosa may ensue

Peripheral Neuritis in Periarteritis Nodosa Clinicopathologic Study is reported by Leonard L Lovshin (Mayo Found) and James W Kernohan[4] (Mayo Clinic) Peripheral neuritis in periarteritis nodosa has been difficult to evaluate clinically because of the arthritis and myositis and pathologically because of the rarity with which peripheral nerves have been studied at autopsy

Records of 25 males and 4 females aged 3 71 (average 44) with incontrovertible periarteritis nodosa were reviewed Average duration of illness was 6½ months the longest being 29 months In 15 patients peripheral neuritis developed some time during the course of the disease and in 7 neuritis occurred at onset The initial

(4) A h I t M d 8 3 1 338 O t b 1948

dioxide combining power No definite toxicity was encountered

It may be asked if the results from use of compound E are superior to those achieved with salicylates The authors believe it is impossible to answer this question definitely at present Despite unavoidable uncertainty and the preliminary nature of data presented it is thought that results in these three patients indicate a definite pattern of response and improvement The three patients reacted with noticeable similarity and the variations in response which occurred appeared related in large part to the differing doses used This pattern of response involved characteristic and sequential disappearance not only of fever tachycardia and polyarthritis but of the increased P R intervals and sedimentation rate Appearance of bradycardia increased appetite and normalization of serum protein were similar in all patients In light of the characteristic responses of rheumatoid arthritis to compound E it is thought that the pattern of response in rheumatic fever is more definite and distinct than it would otherwise have been

Because of the histologic similarity of cardiac vessels and fibrous valves to skeletal muscle and fibrous tissue it is hoped that compound F will have a favorable effect on involvement of the heart in rheumatic fever It is chiefly for this reason that further studies of the effect of compound E in acute rheumatic fever are justified

[The results are not as conclusive as those in rheumatoid arthritis involving only three cases of rheumatic fever nevertheless they are suggestive enough to raise high hopes —Ed]

Periarteritis Nodosa Case of Fatal Exfoliative Dermatitis Resulting from Dilantin® Sodium Sensitization is reported by Judson J Van Wyk and C Rowell Hoffmann[3]

Man 71 was hospitalized in a stuporous state with the primary complaint of ulcerative stomatitis and conjunctivitis Six months before admission he had had three generalized convulsions the first in his life He was treated with dilantin®

(3) Arch Int Med 81 605 610 May 1948

signs of early menopause The episodes have recurred at regular interval of 17 22 days and are accompanied by fever and other symptoms They last five to seven days Menstrual periods occur in regular 27 29 day cycles and have no obvious relation with or influence on febrile attacks Repeated examinations during the past six years revealed no significant abnormalities during free periods Laboratory studies were not helpful The only abnormalities were occasional panleukopenia (2 000 3 000 cells) at irregular intervals not related to the fever con tant monocytosis (between 7 and 21 per cent) a persistently increased sedimentation rate and an increa ed amount of globulin in the blood No cause has been discovered and no evidence of Hodgkin s di ea e neoplastic disease infection neurologic allergic or psychic disturbance or of hereditary influence is present

CASE 2—Man 27 10 years previously noted periods of headache and vomiting every month or two Episodes began with pain in either side of the chest shoulders or abdomen headache aching of extremitie nausea usually vomiting and temperature of 103 F They lasted about two days and were separated by intervals of good health Intervals gradually shortened to 30 day cycles and finally to 7 days All studies including exploratory laparotomy gave no clues as to cause

CASE 3—Man 37 first noted attacks of peritoneal irritation three years previously They recurred at intervals of two to six weeks usually four weeks with good health between them An episode begins with pain in the abdomen tenderness to pressure and colic Temperature rises to 102 F Nau ea and occasional diarrhea occur Leukocytes rise to 12 000 19 000 After 24 36 hours temperature becomes normal but symptoms persist 48-60 hours All studies have been uninformative

CASE 4—Man 20 was discharged from the army because of repeated episodes of leukopenia and disability recurring at 20 22 day intervals and lasting 5 7 days Episodes begin with progressive fall of polymorphonuclear cells for two or three days sometimes to zero accompanied by increasing malaise headache sore throat and aching of the body Tenderness and swelling of cervical lymph nodes and small ulcer on tongue and oral mucosa o cur Symptoms and signs gradually abate and the patient is well until the next episode

CASE 5—Woman 31 has epi odes of pain and swelling of the left knee and stiffness of the right elbow which last 7 days and recur every 13 14 days Fever has not been detected X rays electrocardiogram and laboratory work have all been negative

CASE 6—Man 64 has episodes of evere muscular weak

neuritic symptoms were paresthesias weakness or pain or combinations of these All extremities were involved in 10 patients Involvement of a single nerve was not observed in any patient Involvement was predominantly motor in type but 13 of the 15 patients had both motor and sensory changes

Histologic study revealed involvement of the nutrient arteries of peripheral nerves in 19 patients Such lesions were observed in all 15 patients in whom peripheral neuritis was diagnosed clinically Changes in the nutrient arteries of nerves were in no way different from changes in other arteries of the body In a given nerve severity and stage of the inflammatory process of its arteries varied greatly at different levels

Though an incidence of 52 per cent for neuritis in periarteritis nodosa is higher than that usually mentioned the authors believe that it is accurate Periarteritis should be suspected in any obscure disease in which neuritis develops Presence of renal involvement gastrointestinal symptoms hypertension fever and wasting in a patient with peripheral neuritis should strongly suggest the diagnosis

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DISEASES OF UNCERTAIN ETIOLOGY

Periodic Disease Probable Syndrome Including Periodic Fever, Benign Paroxysmal Peritonitis Cyclic Neutropenia and Intermittent Arthralgia Because of their rarity or because they are overlooked disregarded or mistaken for other conditions certain peculiar benign syndromes which last several days and recur for years at remarkably regular short intervals receive little attention Hobart A Reimann[5] (Jefferson Med College) reports six such cases

Case I—Woman 49 beginning 11 years previously had pells of irritability chilliness and sweating which occasionally forced her to spend a day or two in bed and were mistaken for

(5) J A M A. 136 39 244 Jan 4 1948

signs of early menopause The episodes have recurred at regular intervals of 17 22 days and are accompanied by fever and other symptoms They last five to seven days Menstrual period occur in regular 27 29 day cycle and have no obvious relation with or influence on febrile attacks Repeated examinations during the past six years revealed no significant abnormalities during free periods Laboratory studies were not helpful The only abnormalities were occasional panleukopenia (2 000 3 000 cells) at irregular intervals not related to the fever constant monocytosis (between 7 and 21 per cent) a persistently increased sedimentation rate and an increased amount of globulin in the blood No cause has been discovered and no evidence of Hodgkin s disease neoplastic disease infection neurologic allergic or psychic disturbance or of hereditary influence is present

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CASE 5—Woman 31 has episodes of pain and swelling of the left knee and stiffness of the right elbow which last 7 days and recur every 13 14 days Fever has not been detected X rays electrocardio ram and laboratory work have all been negative

CASE 6—Man 64 has episodes of severe muscular weak

ness lasting 7 10 days and recurring at 14 20 day interval

There is no satisfactory explanation for the regular recurrences of fever neutropenia arthralgia and myasthenia in the cases described or why they take place so punctually and uniformly for so long without interfering with the patients general health The episodic diseases do not coincide with or appear to be related to any known natural intrinsic rhythmic fluctuation such as menstruation estrous cycle of animals hibernation or seasonal variation in number of blood platelets It is possible that they signify some obscure intrinsic cycle in both sexes In each case the periodicity appears to be about seven days or some multiple of seven Since all six patients are under observation duration and outcome of their ailments cannot be stated These cases may be a collection of unrelated medical curiosities but if a common underlying cause can be discovered some or all of them may be grouped as a syndrome of periodic disease with different manifestations

Infectious Mononucleosis with Neurologic Complications Report of Fatal Case is presented by Vera B Dolgopol and George S Husson[6] (Willard Parker Hosp New York City) Infectious mononucleosis until recently has been regarded as a mild disease with few complications and with a uniformly favorable outcome However there are several serious complications in this disease (hepatitis thrombocytopenia myocarditis spontaneous rupture of the spleen and involvement of the central and peripheral nervous system) with instances of fatal outcome from the last three Multiple serious complications may occur in the same patient

Girl 19 was hospitalized because of an illness of three days duration characterized by malaise fatigue backache weakness of the legs sore throat and temperature of 102 F The day before admission photophobia double vision and eyelid swelling developed Generalized lymphadenopathy and splenomegaly were noted the day after admission Neurologic involvement increased steadily in the next few days Reflexes were at first

(6) Arch I t M d 83 1 9196 F b y 1949

sluggish and finally only abdominal reflexes could be obtained Headache stiff neck Kernig s and Brudzinski s signs inability to move the legs and difficulty in swallowing were present by the fifth hospital day and she died the sixth day in respiratory paralysis Heterophil antibody titer had risen from 1 448 to 1 14 336

Microscopic changes in tonsils lymph nodes spleen liver kidneys and adrenals were similar to those previously described in cases of infectious mononucleosis In the brain there were severe degenerative changes in the nuclei of the third and fourth cranial nerves and in the inferior reticular nucleus of the medulla and some degeneration of the Purkinje cells of the cerebellum In the spinal cord hemorrhages were present in the gray matter mainly in the posterior horns but in the lumbar region the hemorrhages had spread into the anterior horns as well

Epidemic of Infectious Lymphocytosis with Diarrhea in 28 patients at Milwaukee County Home for Dependent Children and County Hospital is reported by M G Peterman J D Kaster Eli A Gecht and G L Lembert[7] The disease was first described in the United States in 1941 but since then has been reported in many other countries The paucity of its symptoms and signs suggests that the disease is more common than has been suspected Its interest lies chiefly in the remarkable elevation of white cell count to leukemic levels without outward manifestation in most patients

In the epidemic reported 25 of the 28 children were aged 5 or less Diarrhea was the most prominent symptom and occurred in 16 patients it was usually intermittent and lasted 2 19 days Slight nasal discharge mucous in character and lasting only a few days was noted in six patients There was slight cervical lymph node enlargement in 10 and generalized lymphadenopathy in 4 patients In none were lymph nodes tender Spleen was barely palpable in three patient and liver was palpable in one Four febrile patients never had temperatures over 102 5 F In 10 patients the pharynx was slightly congested for two or three days White cell counts ranged

(7) P d t 3 214 2 1 F bru y 1949

from 18 900 to 147 000/cu mm Peak counts of 90 000 or more occurred in seven Lymphocyte counts ranged from 64 to 94 per cent otherwise differential counts were normal Routine nasopharyngeal cultures afforded no clues as to etiologic agent Incubation period is thought to be two or three weeks

Virus as Possible Etiologic Agent of Erythema Multiforme Exudativum, Bullous Type Report of Case is presented by John A Anderson Vern Bolin Wataru W Sutow and William Kitto[8] (Univ of Utah)

Boy 6½ was hospitalized in a delirious and highly toxic condition Illness had begun three days previously with conjunctivitis Next day fever anorexia and blisters on the lips labial and buccal mucosa and tongue developed The day before admission generalized ra h had appeared

The child s history w s noncontributory The father was susceptible to herpes labialis and had had a severe attack about three weeks before the child became ill

There was a diffuse erythematous macular papular and bullous rash over the entire body Palms fingers soles and toes exhibited massive bullae which yielded a clear fluid free of organisms on direct stain Purulent conjunctivitis was present The child remained acutely ill eight days and then gradually improved All bullae and vesicles desquamated There was no corneal involvement and vision seemed unaffected though photophobia persisted some months

Material taken from skin vesicles on the third and fourth days of the illness produced keratoconjunctivitis on a scarified rabbit cornea and cytoplasmic inclusion bodies were observed in the epithelial and exudative cells of the rabbit cornea Serum of a rabbit recovered from keratoconjunctivitis contained no neutralizing antibodies against the virus of herpes simplex (HF strain)

Review of the literature offers some evidence that the bullous type of erythema multiforme exudativum may be infectious The herpetic nature of the disease the occurrence of epidemics and the failure of all workers to find a common bacteriologic agent also suggest that a virus may be the etiologic agent though a number of investi

(8) Ar h Derm t & Syph 59 51 6 M h 1949

gators have failed in their attempts to find such an agent

Whereas a specific virus was not isolated from this patient certain observations offer evidence that the illness was caused by a virus That the child s illness was preceded by herpetic lesions on the father s lip and that the child himself had herpetic vesicular lesions in his mouth two days before the generalized skin eruption appeared is suggestive Production of a severe keratoconjunctivitis in the rabbit eye which could be transmitted in sterile washings to a second rabbit suggests that a viral agent was present in the vesicular fluid and in washings from the eye Finally the acidophil cytoplasmic inclusion bodies in epithelial cells and monocytic cells infiltrating the limbus of the scarified rabbit cornea inoculated with vesicular fluid furnished additional evidence of a viral agent in vesicular fluid Failure of the agent in the bacteriologically sterile vesicular fluid to produce fatal encephalitis in young Swiss mice was evidence that this agent was probably not the virus of herpes simplex Failure of antibodies to develop against the virus of herpes simplex (HF strain) in the rabbit convalescing from keratoconjunctivitis was also against the possibility that this agent is the virus of herpes simplex Finally the virus of herpes simplex produces intranuclear acidophil inclusion bodies whereas those observed in the rabbit cornea were all cytoplasmic acidophil inclusion bodies

[The virus de cribed appears to be closely related to that of herpes simplex Erythema multiforme i probably a syndrome which can result from a variety of circumstances it can occur with sulfonamide sens t vity among other things —Ed]

Epidemic Myalgia A M Harvey P A Tumulty F B Bang and W B Leftwich[9] observed a small epidemic at Johns Hopkins Hospital in October and November 1947 in which pleurodynia and cervical myalgia appeared concurrently at times in the same person

Epidemic pleurodynia is characterized by paroxysmal pain in a muscle or group of muscles Pain begins sud

(9) South M J 41 73 736 A gu t 1948

denly and may be sharp and knifelike or dull and aching It is usually localized to the lower chest and epigastrium and is aggravated by any action that causes contraction of thoracic or abdominal muscles such as deep breathing coughing or sneezing Pain may radiate to the back shoulders or abdomen Temperature may rise suddenly to 102 or 103 F and fall rapidly to normal in 12-48 hours

It has been suggested that the common condition of stiff neck is a localized infectious myalgia It usually begins suddenly is confined to one side of the neck and abates after 12-48 hours but may persist in a mild form for days or weeks Acute myalgia of the neck and shoulders was described in 125 patients in England during the winter of 1941-42

In the epidemic described by the authors about 30 patients had pleurodynia and a small number had acute torticollis Though the relation between pleurodynia and cervical myalgia has been suggested previously other observers have regarded the two conditions as distinct entities because of the predominance of trapezius involvement and absence of pleural pain fever and leukocytosis in cervical myalgia Cervical myalgia has however been commonly reported in epidemics of pleurodynia

[One might argue with the conclusion that cervical myalgia and pleurodynia are varieties of the same disease because both clinical pictures were seen in a single epidemic —Ed]

Reiter's Disease Study of 344 Cases Observed in Finland is presented by Ilmari Paronen[1] (Univ of Helsinki) Reiter s disease may be defined as a syndrome of unknown etiology characterized by three essential symptoms arthritis conjunctivitis and urethritis It is usually postdysenteric Its frequency during epidemics of dysentery varies greatly the lowest and the highest incidences reported being 0 27 and 10 per cent Many names have been given the disease Reiter s disease or syndrome and dysenteric arthritis being most frequently used Any

(1) Acta med S d nav (pp 1) 131 1 114 1948

one of the three essential symptoms may initiate the disease The triad does not evolve in all cases and the disease may occur with two or even one essential symptom However ocular and urethral lesions seem to occur relatively seldom alone or together as the only sign of the syndrome In contrast joint lesions are often the only symptom and in such cases diagnosis is based on the fact that the joint disease appeared after dysentery or that cases of dysentery and Reiter s triad had occurred in the environment

Joint affections generally appear after symptoms of dysentery have subsided most often within two to four weeks from onset of dysentery Arthritis is generally polyarticular joints of the lower extremities being more commonly affected than tho e of the upper and large joints more often than small joints Articular suppuration has not occurred Duration of arthritis varies though it may disappear within a few days it generally lasts for weeks or months

Conjunctivitis either bilateral or unilateral seems to be the most common ocular manifestation though iritis keratitis corneal ulceration and iridocyclitis have also been described Conjunctivitis generally lasts a few days or weeks Urethritis is the commonest type of urinary tract involvement Urethral discharge is less profu e than in acute gonorrhea and is usually observed only on pressure on the penis Lesions of the nervous system have been observed in Reiter s syndrome the most common being neuritis There is disagreement regarding occurrence of cardiac complications in thi syndrome some writers statin that heart complications are lacking and others that endocarditis and valvular disease do not occur but that myocarditis does Many types of skin lesions have been described in connection with this syndrome but whether they can be ascribed to it or are concurrent lesions due to other causes is not known Differentiation of Reiter s di ease from keratosis blennorrhagica and from the Stevens Johnson syndrome may be difficult

Fever may be high slight or lacking Sedimentation rate is usually elevated and most patients show leuko cytosis Both Wassermann and gonococcus complement fixation tests are negative Some writers have reported negative serum agglutination tests for dysentery and others positive agglutination tests for the Shiga Kruse or Flexner groups

Diagnosis of Reiter s disease is not generally difficult as it is readily distinguished from other joint diseases by associated symptoms Prognosis is good No deaths have been reported and in general no permanent or dis abling changes occur in affected organs Duration of dis ease is two to five months and recovery is usually spon taneous

Most writers have thought that Reiter s syndrome is causally related closely to dysentery Yet it is evident that in some cases there has never been dysentery or enteritis It is therefore assumed that dysentery is the most usual but not the sole cause Pleuropneumonia like organisms have been isolated from prostatic o urethral discharges in five patients with Reiter s disease Further bacteriologic study of this disease should be made A few writers have suggested that its pathogene sis can be explained on the basis of allergy analogous to that of rheumatoid arthritis

Most of Paronen s 344 cases originated in a wide spread epidemic of Flexner s dysentery on the Karelian Isthmus during the war operations in the summer of 1944 There were 310 men aged 18-40 and 34 women About 70 per cent manifested the complete triad (articu lar ocular and urethral manifestations) about 25 per cent two of the essential symptoms and 5 per cent only one Articular manifestations were observed in 325 cases eye affections in 298 and urogenital involvement in 265 Fever occurred in 260 patients (axillary temperature over 98 6 F) Duration of fever varied from one day to six months Articular symptoms in most cases disap peared within a few months but in some were observed

as late as one to three years after treatment No medication (salicylates pyramidon* aspirin salvarsan sulfonamides etc) fever therapy or radiation led to prompt and general recovery The course seemed self limited

Of the 334 patients 322 had had Flexner s dysentery and only 12 contracted Reiter s disease without previous diarrhea Estimated number of persons affected by the dysentery epidemic during the study period was 150 000 Accordingly about 0 2 per cent of them contracted Reiter s disease a slightly lower incidence than that reported in the literature In two third Reiter s disease set in within 11 30 days from onset of dysentery but the former occasionally began simultaneously with the latter or even before it Longest interval was over three months There was no apparent relationship between Reiter s disease and severity of dysentery

Blood Wassermann and Kahn reactions and the gonococcus complement fixation test were negative Serum agglutination tests for typhoid paratyphoid typhus and Brucella abortus Bang also gave negative results However 61 of 132 examined serums agglutinated a Flexner A + D + WX suspension in titers of 1 80 1 640

Paronen concludes that this study justifies the conclusion that Reiter s syndrome occurs only after dysentery and that the dysentery bacillus seems to be the causative factor even when no dysenteric infection can be demonstrated by clinical means

[This must be the large t series of cases observed by one physician it adds weight to the hypothesis that the syndrome is a sequel of bacillary dy entery Studies for pleuropneumonia organisms were not made The o ginal contains many u eful details on the various clinical manifestations —Ed]

Autoantibodies in Human Glomerulonephritis were studied by Kurt Lange Michael M A Gold David Weiner and Vera Simon (New York Med College) It has often been suggested that the cour e of human glomerulonephritis could be explained by an antigen antibody reaction The 10 20 day interval between primary

( ) J Cl n Inv t gation 28 50 55 J y 1949

streptococcic infection and first signs of nephritis absence of streptococcic invasion of the kidney and the severe general involvement of the glomerular apparatus suggest this possibility Chronic glomerulonephritis can be produced by injection of heterologous immune antikidney serum Such antibodies are selectively adsorbed from the circulation by the kidneys and cause specific changes in the kidney

The authors devised a modified collodion particle technic for detecting antibodies to kidney tissue *In this* test kidney emulsions are mixed with collodion suspensions and used as antigens Serial dilutions of serum from patients with glomerulonephritis are set up in serologic test tubes containing this antigen solution

By this method antibodies to human renal tissue were demonstrated in 75 per cent of 122 tests done on the blood of 23 patients with glomerulonephritis In 12 patients with early nephritis 68 per cent of the determinations done were positive In 11 patients with late nephritis *78 per cent of determinations were positive* Antibodies to human renal tissue were found in 19 per cent of 126 determinations done on 68 controls Renal antigens from infants or stillborn infants show greater specificity and higher titers than antigens from adult renal tissue

The possibility of neutralizing these antikidney antibodies provides an avenue of approach to the therapy of glomerulonephritis

[Reports of finding of antibodies to kidney or heart in patients with glomerulonephritis or rheumatic fever continue to appear *till the case for this concept is not absolutely convincing* The collodion particle serologic technic is very tricky —Ed]

NUTRITION AND INFECTIOUS DISEASE

Etiology of Ekiri Highly Fatal Disease of Japanese Children Ekiri is a highly fatal disease of the Japanese in the age group of 2 6 years which is prevalent in the

summer Clinically ekiri is characterized by sudden onset with high fever diarrhea vomiting and convulsions and a short course death occurring in 4 48 hours Bacteriologic studies by Japanese workers have yielded dysentery bacilli from stools of about half the patients and changes compatible with early bacillary dysentery have been found in such patients at autopsy Bacillary dysentery is common in Japan during the summer Despite these suggestive facts the high fatality rate of ekiri predominance of convulsions extreme fever and failure to isolate dysentery bacilli in many typical cases suggested the disease was not dysentery or that some additional factor was involved

In the summer of 1947 under the auspices of the Japanese Institute of Health and Supreme Command of the Allied Forces an American team studied ekiri in Japan Katharine Dodd G John Buddingh and Samuel Rapoport[3] report their findings

The clinical history of ekiri was that described in many Japanese articles Children aged 2 6 became suddenly ill with high fever often 104 9 F or more diarrhea which was usually bloody vomiting extreme lethargy alternating with irritability yawning spells and convulsions which occurred some hours after onset of other symptoms The children lay quietly in bed often in a semi comatose state Muscles of the face looked stiff the eye slits narrow both because of periorbital edema and spasm of the periorbital muscles Lips were pursed and curved with trismus on crying Spontaneous twitching of facial muscles neck and extremities was often visible Hyperventilation and generalized muscle spasm occurred

If the child survived the early stage and began to improve temperature fell diarrhea diminished or ceased vomiting stopped and muscles relaxed At this stage classic signs of tetany Chvostek s Trousseau s and peroneal signs could be elicited easily

(3) P d . 3 9 19 J y 1949

The authors began to examine children believed to have dysentery rather than ekiri The outstanding difference between the groups seemed to be severity of tetany rather than severity of dysentery infection

Serum calcium of the children was low and calcium treatment was begun Because of severity of tetanic manifestations and vomiting calcium chloride was used intravenously Effects in patients in early stages were spectacular When the child had received about 5 cc of 10 per cent solution of calcium chloride he began to relax move his arms and legs and seemed surprised he could move so easily again Repeated administration of calcium would check tetany and allow some children with ekiri to recover

During the summer cultures were made from stools of 106 patients Approximately two thirds were believed to have ekiri and one third dysentery Of the 106 cultures 95 contained dysentery bacilli Of these 42 were Shigella sonnei 32 were Shigella of Flexner 20 were Shigella ambigua and 1 Shigella dysenteriae Salmonella Shigella medium and large inoculums were used for stool culture The fact that the Japanese use only Endo s medium for culture and usually inoculate with a small amount of stool seemed the probable explanation of their failure to obtain positive stool cultures in many patients

Autopsies were performed on 29 children Gross pathologic changes found in 24 were those of bacillary dysentery There was edema of the colon and slight ulceration lungs were emphysematous and sometimes edematous with subpleural hemorrhage and occasional hemorrhages into alveoli Gastric mucosa was congested and bleeding Brains were edematous and heavy with flattening of convolutions and much subpial edema

From clinical observations three disturbances of body function emerged to the foreground tetany hyperventilation and dehydration From clinical observations plus blood chemistry studies a hypothetical picture of ekiri may be drawn in which a pre existing tendency to hypo

calcemic tetany has a leading role Japanese children drink little milk and hence diet is low in calcium Estimated calcium consumption of children aged 3-6 ranges from 0 1 to 0 15 Gm daily although in other respects diet seems fairly satisfactory Tetany made manifest by infection is thought to be the basis of the unusual degree of hyperventilation and fever observed

To explore the possibility of latent tetany 29 well Japanese children were examined Almost all had Chvostek s sign and about half of them had some twitching of muscles or Trousseau s sign of hands or feet

From a clinical bacteriologic chemical and pathologic standpoint it was concluded that ekiri is mostly bacillary dysentery complicated by tetany It represents a disease complex where underlying nutritional and chemical factors determine the course manifestations and prognosis of an infectious disease in contrast with the relationship usually observed where (as in infantile diarrhea) chemical disturbances are secondary to the infectious process The fulminating character of ekiri the rapid advent of irreversible changes and frequent delay in initiation of treatment all conspire to lessen effectiveness of therapy Prevention offers the greater promise Aside from obvious measures to decrease incidence of dysentery an increase of calcium in the diet would rob dysentery of its specific malignant features in Japan Ideally such an increase in calcium supply would be best accomplished by increasing milk intake

[A very satisfying piece of clinical sleuthing —Ed]

Electrocardiographic Changes in Typhoid Fever and Their Reversibility Following Niacin Treatment M Rachmilewitz and K Braun* (Jerusalem) report electrocardiographic studies on 50 patients with typhoid fever treated during the past three years With a single exception all were without clinical evidence of previous heart disease The cou se was moderately severe in most patients and there were no fatalities Serial electro

(4) Am H t J 36 284 294 A g t 1948

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slants of endameba medium Tubes were then incubated at 37 C and observed every 24 or 48 hours for 14 days Effect of streptomycin calcium chloride complex was studied by adding varying amounts of the drug to culture tubes at time of inoculation Use of streptomycin increased number of cultures in which trophozoites were found from 8 per cent in controls to 73 per cent Of 26 control cultures only 2 yielded E histolytica whereas of 26 cultures to which streptomycin had been added 18 were positive

Hemagglutination Test for Diagnosis of Influenzal Meningitis The test described by M F Warburton E V Keogh (Parkville Victoria) and S W Williams[6] (Melbourne) is based on a recent observation that polysaccharides of many species of bacteria including Hemophilus influenzae are adsorbed from their solutions to the surfaces of red blood cells Erythrocytes so coated are agglutinated by serum containin antibody to the particular polysaccharide The test is more sensitive than previously used precipitin reactions for detection of the specific polysaccharide of H influenzae in pinal fluid although it does not differ in principle from the method of diagnosis in which the precipitin reaction between the polysaccharide in the cerebrospinal fluid and the specific antiserum is utilized In addition it gives a direct quantitative measure of the concentration of polysaccharide and thereby provides a means for assessing severity of the infection and possible response to therapy

It has the further advantage of permitting diagnosis of influenzal meningitis to be confirmed or excluded with certainty within an hour of receipt of a specimen of spinal fluid in the laboratory Importance of early institution of specific therapy in this disease is well known

Thymol Turbidity Test in Acute Infectious Di eases was investigated by Kurt Iversen and Flemming Raaschou (Copenhagen) A number of investigators have

(6) M J A t 1 1 135 137 J 29 1949
(7) A I I t M d 8 251 S pt mb 1948

cardiograms were made on admission and at frequent intervals during the disease and during convalescence Standard limb leads and precordial lead IV F were recorded

Fifteen patients showed no electrocardiographic changes on repeated examinations and 35 showed alterations Age incidence in the two groups was not significantly different The most conspicuous changes were found in the T waves All 35 patients showed some degree of abnormality in the T waves which were of low amplitude isoelectric or diphasic No clinical cardiovascular disturbances or subjective complaints referable to the heart were noted in the patients with ECG changes

Since in most patients the T wave alterations appeared with clinical signs of vitamin B deficiency and since the ECG changes resembled those seen in niacin deficiency 23 patients were given niacin in daily oral doses of 300 600 mg and in some cases intravenously also Treatment was begun after ECG changes had become pronounced and constant All electrocardiograms improved greatly within 10 days most of them within 2 5 days The authors believe that the rapid change indicates that electrocardiographic changes were due to niacin deficiency

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LABORATORY TESTS

Use of Streptomycin in Cultivation of Endamoeba Histolytica from Stools was studied by Clifford L Spingarn and Morton H Edelman[5] (New York City) For the experiments 20 stool specimens containing cysts of E. histolytica were obtained from the New York City Health Department and from patients at Mount Sinai Hospital Heavy stool suspensions were prepared with normal saline and 3 drops of this suspension was added to the horse serum normal saline solution overlying

(5) Am J Trop Med 8 8 589 November 1948

action as well as signs of hepatic damage according to the sulfobromophthalein sodium test

Results of this study indicate that the thymol reaction in measles infectious mononucleosis and hepatitis indicates certain changes in serum globulin These may be directly connected with antibody production Whether the changes are qualitative or quantitative is not known Thymol reaction is probably not a proper test of hepatic function

[Lymphogranuloma venereum is another infectious disease in which the thymol turbidity test is strongly positive —Ed]

IMMUNIZATION

Early Whooping Cough Immunization Salmon R Halpern and Doris Halpern[9] evaluated effects of vaccination *against whooping cough in infants seen in well* child conferences sponsored by the city of Dallas since 1946 Vaccine used was phase I of Hemophilus pertussis alum precipitated and standardized to contain 40 billion organisms/cc Doses of 0 2 0 3 and 0 5 cc were given at four week intervals Some infants received the first injection at age 2 weeks but immunization was usually begun at age 1 month Reaction to immunization was evaluated by use of skin and agglutination tests before and after immunization Skin tests were negative in 115 of 117 infants before immunization was started and agglutination tests were negative in 101 of 117

Among 112 of 115 infants in whom immunization was completed before age 4 months skin tests done after completion of immunization were positive and agglutination *tests strongly positive in 68 weakly positive in 37* and negative in 10 In 56 of 60 infants whose immunization was completed between ages 4 and 6 months skin tests after completion of immunization were positive

(8) J P d t 33 43 48 J ly 1948

found the thymol turbidity test positive in about 90 per cent of cases of acute hepatitis and usually positive in chronic hepatitis but rarely positive in bile duct obstruction and hepatic cancer The fact that possible changes in serum gamma globulin might determine the result of the thymol test led to investigation of the thymol test in acute virus diseases since the course of measles and mumps is known to be altered by administration of gamma globulin

The authors performed the thymol turbidity test on 373 persons with different acute infectious diseases Reaction was positive in 71 per cent of 45 patients with measles In the majority the reaction began to be evident at onset of cutaneous eruption and remained positive for greatly varying periods In a few cases reaction became negative by the twenty second day Other tests of hepatic function made whenever reactions to thymol turbidity were highly positive gave negative results The thymol test may be useful for differentiation between measles and other conditions with morbilliform eruptions

Of 34 patients with infectious mononucleosis thymol turbidity test was positive in 26 and Paul Bunnell reaction positive in 27 Thymol test reaction was negative in tonsillitis scarlet fever mumps serous meningitis pneumonia purulent meningitis tuberculous meningitis and acute gastroenteritis

The fact that a positive reaction to the thymol test is seen not only in hepatitis but also in measles shows that a positive reaction is not exclusively a criterion of hepatic damage Hepatitis is not associated with measles and tests of hepatic function never revealed signs of hepatic damage in these patients What the positive thymol reaction in infectious mononucleosis indicates is uncertain hepatitis was manifest in only one case and other tests of hepatic function were negative Other authors have described patients with infectious mononucleosis without jaundice all of whom presented a positive thymol re

About 25 000 of the persons vaccinated returned for a reading of the vaccination site and notes were made of reactions obtained When there were good vesiculation and scab formation vaccinations were listed as successful Of this sample of 25 000 persons 73 6 per cent had successful reactions and 26 4 per cent immune reactions These results indicate a high susceptibility to smallpox in the sample surveyed Since the group came from all health centers in the city and was fairly representative as to sexes age groups and races it is fair to assume that it represented a cross section of population An even higher degree of susceptibility to smallpox was found among 7 380 students and teachers at New York University 3 117 of whom returned for readings Of these 93 per cent had positive takes 2 per cent were immune and 5 per cent had no reactions These samplings indicate low immunity to smallpox in New York City and need for widespread vaccination when an epidemic threatens

Next to postvaccinal encephalitis the commonest and most serious complication was generalized vaccinia [Occurrence of postvaccinal encephalitis in this group is described in detail in the following article —Ed] This term is used by some authors to indicate widespread vaccinal rash in absence of a pre existing dermatosis Some authors believe that presence of a pre existing eczema means that the vaccinia has been spread by contact rather than by the blood stream but there seems little evidence to support this concept Vaccinia virus enters the blood stream soon after vaccination and the rather rapid generalized and simultaneous distribution of lesions argues for a general spread by the blood stream In the present study all cases in which a general spread of vaccinal lesions occurred irrespective of whether there was a pre existing rash or not are included under generalized vaccinia Cases in which there was spread of vaccinal lesions only in the vicinity of vaccination or in adjacent areas are excluded

Forty five cases of generalized vaccinia occurred

and agglutination tests were strongly positive in 45, weakly positive in 14 and negative in 1

Of 161 patients 110 had no side reactions to immunization. Reactions occurring in the others included fever, induration and in three instances abscess formation. During the two years of this study none of the infants was reported to have contracted whooping cough.

The authors recommend the agglutinogen skin test as a simple, reliable and specific means of evaluating results of immunization.

Human Antibody Response to Simultaneous Injection of Six Specific Polysaccharides of Pneumococcus. Previous quantitative studies of antibody content of serums of human beings given injections of specific polysaccharides of pneumococcus in immunizing doses have dealt with analyses of serums after injection of two or three and four specific polysaccharides at one time. Michael Heidelberger, Colin M. MacLeod and Marie M. Di Lapi[9] (New York City) combined into a single solution six polysaccharides of the pneumococcus types most commonly responsible for pneumococcic pneumonias in man to determine antibody response to injection of so many chemically similar antigens. Total antibody response and production of antibody to each antigen injected appeared to be as satisfactory as in subjects treated with smaller numbers of polysaccharides.

[Immunization with pooled pneumococcus polysaccharide is worth consideration in patients who have repeated attacks of pneumonia; for example, some patients with bronchiectasis might benefit from it.—Ed.]

Complications of Vaccination against Smallpox are described by Morris Greenberg[1] (Dept. of Health, New York City). Vaccination of approximately 5,000,000 persons in New York City in about a month after discovery of a case of smallpox in March 1947 presented an opportunity to study results of vaccination in a large group from the viewpoint of possible complications.

(9) J. Exper. Med. 88: 369-3..., September, 1948.
(1) Am. J. Dis. Child. 6: 49-50, November, 1948.

ease Research Laboratory tests There were 12 positive reactors an incidence of 9 per cent

Considerable evidence has accumulated to indicate that trauma due to various factors experienced by a woman during pregnancy may influence viability or development of the fetus After vaccination against smallpox vaccinia virus enters the blood stream and is disseminated to the tissues of the body The question has therefore arisen whether pregnant women should be vaccinated against smallpox and if they are what the chances are of their giving birth to a child with congenital defects Preliminary observations indicate that vaccination is a safe procedure during the first four months of pregnancy so far as occurrence of congenital defects in offspring is concerned

Postvaccinal Encephalitis Report of 45 Cases in New York City Soon after approximately 5 000 000 persons were vaccinated in New York City and for two months thereafter all reported cases of encephalitis poliomyelitis and other neurotropic diseases were carefully investigated Diagnosis of postvaccinal encephalitis made on clinical grounds is a presumptive diagnosis Not only is there no difference between the clinical picture of this disease and that of other encephalitides but there is often little to distinguish it from brain tumor and tuberculous meningitis

Morris Greenberg and Emanuel Appelbaum[2] (Dept of Health New York City) found 49 cases diagnosed as postvaccinal encephalitis Eight were fatal and autopsy was done in all Tuberculous meningitis was found in two brain tumor in one and hypertensive vascular disease with coronary occlusion and congestion of the brain in one The other 45 cases were accepted as true cases of postvaccinal encephalitis

Average incubation period was 10 12 days Clinical picture was variable Onset was generally abrupt with fever headache vomiting and changes in mental state

(2) Am J M S 16 565 5 0 \ mb 1948

Laboratory confirmation was attempted in 15 cases and vaccinia virus was recovered in all by growth on chick embryo Most lesions occurred in persons with pre exist ing eczema 38 of the affected persons having had eczema preceding generalized vaccinia What is more significant is that 28 of those with eczema had not been vaccinated All but one had been exposed intimately to one or more persons who had recently been vaccinated Two infants neither of whom had been vaccinated died The conclu sion is justified that infants with eczema should not be vaccinated until the skin has cleared Furthermore no person taking care of an infant with eczema should be vaccinated unless special precautions are taken to prevent contact of the eczematous child with the vaccinated site Though more than three fourths of ca es of generalized vaccinia occurred in children under age 5 no age group is immune

The commonest complaint was painful arm with regional lymphadenopathy occurring chiefly in persons with uncomplicated takes Local infections were occa sionally seen and generalized macular papular and urti carial lesions were observed The only serious infection resulting from vaccination was cellulitis of the arm from which septicemia developed and death occurred one month after vaccination

Tetanus used to be a bugaboo of vaccination but ad vances in care of vaccinated calves in collection and preservation of lymph and in tests for contamination have made vaccine virus a safe product Elimination of dressings over vaccinated areas has further minimized chances of deep implantation of accidental infection by retained exudate Not a single case of tetanus occurred in New York City as a result of vaccination

It has previously been reported that false positive serologic reactions for syphilis occur after vaccination in some persons Specimens of blood from 133 known nonsyphilitic subjects who had been vaccinated were tested by the Mazzini Kahn Kolmer and Venereal Dis

The same day the patient was drowsy and febrile (101 F) Examination revealed no abnormalities except a few rhonchi in the chest and slightly enlarged axillary and inguinal lymph nodes The next day however temperature was 104 6 F and catheterization was necessary The following day flaccid paralysis of legs was present Abdominal muscles became paralyzed and finally the patient had to be placed in a respirator At times he was delirious Shoulders and arms were then found to be paralyzed Lumbar puncture revealed clear spinal fluid containing 100 mg per cent protein and 110 cell /cu mm of which 64 per cent were lymphocytes and 36 per cent large mononuclears He died four days after onset of illness Autopsy revealed acute disseminated myelitis extending into the brain stem but not into the cortex of the cerebrum or cerebellum

Incidence of neuroparalytic accidents after all types of antirabic vaccines has been estimated to be 1 in 5 814 cases Mortality among these cases is about 25 per cent Onset usually occurs 13 15 days after beginning of therapy and may take one of four forms ascending paralysis of the Landry type transverse myelitis mononeuritis or multiple neuritis involving cranial or peripheral nerves or meningoencephalomyelitis

The virus and toxin theories of etiology of neuroparalytic accidents after rabies vaccine have been replaced to a large extent by the allergic theory which is based on the experimental production of disseminated neurologic lesions in monkeys by inoculation of normal heterologous nerve substance

If a patient who is to be given antirabic vaccine has a family or personal history of allergy skin tests for sensitivity are indicated If excessive skin reactions occur during treatment desensitization should be considered

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FEVER

Why Are Fever Temperatures over 106 F Rare? High temperature in itself can damage tissues but it is hard to estimate the level at which each particular organ is injured Exceptional patients have survived tempera

Occasionally initial symptoms were followed by a remission lasting 24 72 hours after which symptoms progressed Fever was usually slight in mild cases and was accompanied by dizziness irritability ataxia and personality changes In more severe cases hyperpyrexia delirium convulsions coma and stupor occurred Most patients showed signs of nuchal rigidity with Kernig s and Brudzinski s signs Paralyses of the extremities were not unusual and retention of urine was frequent Changes in deep and superficial reflexes were variable in some exaggerated and in others diminished or absent Clinical course was usually short recovery occurring completely in one or two weeks Of the 41 patients who survived 38 made complete recovery 1 had residual hemiparesis and 1 residual optic neuritis six months after onset 1 could not be followed up Spinal fluid examinations done on all but three patients usually showed clear fluid under pressure In 16 cases the cell count was less than 10/ml In the others average cell count was 100/cu mm predominantly lymphocytes

Pathologically the distinctive lesions of postvaccinal encephalitis are in the brain and spinal cord and consist of areas of softening in which demyelination can be demonstrated histologically White and gray matter are both involved Autopsy in the four fatal cases showed no such lesions In two cases the only lesions were marked congestion of the brain In the other two cuffing of vessels in brain and spinal cord was demonstrated but no demyelination was present Although these four deaths are ascribed to postvaccinal encephalitis definite pathologic proof is lacking Attempts to recover virus from brains in three cases were unsuccessful

Fatal Case of Myelitis after Antirabic Vaccine is reported by I Ansell[3]

Man 26 was given an antirabic injection *daily for 12 days* starting 2 days after he was bitten by a healthy puppy Because the dog remained healthy treatment was discontinued

(3) B t M J 2 338 340 A g 14 1948

the temperatures differ markedly from those found in infectious diseases Probably the hyperthermias that have impressed clinicians are the terminal high tempera tures of moribund patients Under certain special condi tions it is possible to obtain very high temperatures in fever If intravenous injections which contain pyrogens are given to fever patients the results may be dramatic

Thus temperature rises over 106 F in the presence of (1) a sudden overwhelming heat load as in a fever cabinet or the chill from pyrogens (2) a prolonged overwhelming load with exhaustion of the sweat glands as in heat stroke (3) failure of the circulation and/or failure of the temperature regulating mechanism in mori bund patients (4) some infectious diseases with occa sional readings between 106 8 and 107 6 F

It is evident that in fevers the great majority of read ings are below 106 F which is safely below the point at which temperature itself is dangerous Everything points to a temperature regulating mechanism that functions well at the thermostatic level set by the particular stage of the disease The sharp limitation of temperatures at the level of about 106 F points toward an emergency regulatory mechanism in fever that protects the body with great efficiency

tures of 113 F (45 C) but not many live more than a few days or weeks after temperature has reached 107 F From the work of fever therapists it is known that persons in good condition can stand 107 6 F for 8-10 hours but this is close to the upper limit of tolerance Temperatures within 2 degrees of this danger level are seldom found in fever

Eugene F DuBois[4] (Cornell Univ) believes that the known facts can be best explained by assuming that the temperature regulating mechanism functions well at the higher thermostatic level set by the particular disease There must be an emergency mechanism that strongly resists the approach to levels that threaten life

Temperature around 104 F cannot be regarded as dangerous or even deleterious inasmuch as it is the level found in athletes during hard exercise Muscles are most efficient at this temperature Patients in good condition adjust well to moderate fever

A survey of 1 761 temperature readings in 357 patients *with diseases characterized by high fever revealed that* only 75 readings were above 106 F and none was above 107 8 F This suggests that there is an automatic cut off that stops rise of temperature before it reaches the level at which high temperature in itself menaces life, a mechanism that prevents body temperature from rising above 106 F

There are however several special conditions in which body temperatures do exceed 105 8 F In fever therapy if the patient is put in a cabinet and heat loss through skin prevented body temperature rises progressively Another cause of severe hyperthermia is heat stroke A third condition that exhibits temperatures above 106 F is the moribund state a few hours before death A great deal has been written about abnormally high temperatures with brain injuries or tumors involving the hypothalamic region Limited study of many cases reported in the literature revealed no evidence that

(4) Am J M Sc 17 361 368 Apr 1, 1949

The Chest

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J BURNS AMBERSON MD

PART II
THE CHEST

ANATOMY OF LUNG

Anatomic Guide to Intersegmental Plane I[illegible] Ramsay[1] (Tufts College) states that pulmona[illegible] are segmental and intersegmental and that th[illegible] are small and closely accompany segmental art[illegible] bronchi Intersegmental veins do not accomp[illegible]

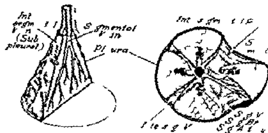


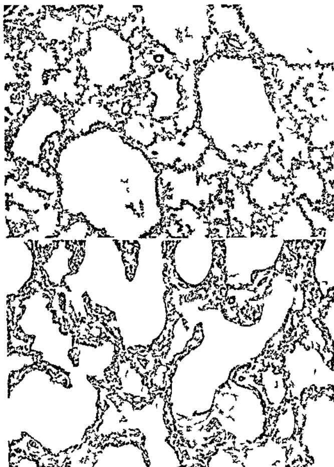
Fig 18 (left) —Diag[illegible] [illegible] pulmon[illegible] [illegible] Fig 19 (right) —D[illegible] [illegible] Segmental [illegible]

(Cou[illegible] [illegible] R[illegible] [illegible] S[illegible] 25 533 538 Ap 1 1949)

structures and can be located in the hilus and follo[illegible]ed distally as accurate guides to the intersegmental plane in all pathologic conditions Thus a simple technic can be followed in segmental resection of practically all bronchopulmonary segments These venous guides are mo[illegible]t valuable in removal of individual basal segments upper lobe segments and subsegments

Figures 18 and 19 show that lungs are composed of in

(1) S[illegible] 25 533 538 Ap 1 1949



F g 20 (t p) —L g g l l l ta fi d to l w l tt l b f th rw rm l l g f f ll m f t C mp th p m y on g t l d l ta on w h q d d l tat f g l l l d pl (F g 1) E m thyl bl × 9)
F g 1 (b tt m) —L g g tal l l dy pl d bl d l t t f m l l p t t f t l l t m l m l t n m l l f p p t t th t t d t l g t f Eo m thyl bl 90
(Cou t y f M M h H E Am J P th 4 919 931 J ly 1948)

dividual units consisting of a central segmental artery bronchus and vein leading into a cone of alveolar tissue The periphery of the cone features several subpleural veins carrying blood centripetally toward the hilus When such individual segments are combined to form lobes surfaces of contact lose their pleural covering and the veins become intersegmental These intersegmental surfaces become flattened by contact and lobe and segments undergo alterations in shape varying with intrathoracic position

By following intersegmental veins peripherally from the hilus surgeons can enter intersegmental planes accurately avoid injury to lung tissue almost eliminate leakage of air from alveolar damage and greatly diminish infection from the exposed parenchyma Incidence of complications such as inexpansible lungs empyema and bronchopleural fistula should not be higher than for an uncomplicated lobectomy Segmental resection permits removal of all damaged or diseased tissue and conservation of all functional normal tissue the ideal in excisional surgery

[This study is very pertinent in view of the increasing frequency of segmental surgery which has proved highly effective in carefully selected cases for removal of diseased sections of the lung while preserving healthy functioning sections As a rule the disease such as bronchiectasis or abscess should be chronic and well localized in a given segment or segments —Ed]

Congenital Alveolar Dysplasia of Lungs H Edward MacMahon (Tufts College) reports on autopsy in three cases Clinically all patients were thought to have fetal atelectasis This anomaly is characterized by defective and hypoplastic development of pulmonary alveoli which in extreme cases causes death in the first 48 hours Typically the picture consists of respiratory distress and progressive intractable cyanosis in a full term child Etiology of retardation of alveolar development is unknown Retardation varies in extent and degree

Grossly the lungs are well formed but almost airless and sink when placed in water Histologically there are

(1) Am J Path 4 919 931 July 194

condition to know that death is due to a developmental anomaly and not to some error in management

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NORMAL AND ABNORMAL PHYSIOLOGY

Pulmonary Atelectasis in Stuporous States Study of Incidence and Mechanism in Sodium Amytal* Narcosis Roy Laver Swank and Magnus I Smedal[3] (Boston) studied frequency character and mechanism of pulmonary changes during deep sodium amytal* narcosis in approximately 350 young men with combat exhaustion The patients were kept in a narcotized state for 5 days deep sleep being attained twice in each 24 hours No patient was narcotized if evidence of infection was present

During deep narcosis all patients showed generalized and uniform decreases in aeration of the lungs symmetrical elevation of the diaphragm and collapse of the chest cage Many (18 of 28 carefully studied) also exhibited focal pulmonary changes of varying severity asymmetrical collapse of the chest and asymmetrical elevation of the diaphragm Some focal lesions showed up in x rays as irregular hazy densities some as linear shadows and one occupied the middle lobe and resembled pneumonia Fever was present at some time in nearly all patients but was usually higher in patients with both focal and general lung changes Most pulmonary changes disappeared within 24 hours but in two patients the lesions remained after narcosis for 4 and 6 days In the absence of infection changes observed are compatible with lobular or segmental atelectasis

Changes leading to atelectasis developed according to a definite pattern and decreased aeration was the first detected change It was due to uniform compression of lung tissue by the collapsed chest and high diaphragm Vascular stasis or congestion contributed to increased density Gross focal pulmonary lesions developed next

(3) Am J M d 5 10 2 9 A g t 1948

few alveoli and far too much interstitial tissue Some of the spaces are very small whereas others are so distended as to suggest congenital alveolar ectasia (Fig 20) Most alveoli are empty but some contain hyaline or granular eosinophilic material (Fig 21) Cornified cells suggesting aspiration of vernix are not found There is no demonstrable basement membrane and much of the alveolar surface is bare of epithelium Interstitial mesenchyme is composed of undifferentiated fibroblasts in a scarcely detectable ground substance Sections prepared with Mallory s acid fuchsin aniline blue stain show well formed collagen fibrils in the pleura and interlobular septa and around large vessels and bronchi but fail to reveal mature collagen in alveolar walls Usually collagen is easily demonstrable in walls of normally developed alveoli Absence of elastica in alveolar walls is not surprising since elastic fibrils are rarely found in alveoli at this age

A second but inconstant and less conspicuous observation is exaggerated demarcation of lobules by abnormally wide septa composed of fibroblasts a little collagen dilated capillaries and lymphatics This rather simple picture of a lung showing too much stroma and too little air space may be complicated by congestion edema hemorrhage aspiration of amniotic fluid or infection

Histologic structure of the lung resembles that seen in the 3–4 month old fetus and therefore suggests retardation of development It differs however from the picture in the fetus in that the capillary bed is greater alveolar epithelium more closely resembles that in mature lung bronchial epithelium is well developed and there is uneven distribution of alveoli in interstitial tissue The principal resemblance between the lung with congenital alveolar dysplasia and that of the 3-4 month old fetus is presence of primitive mesenchyme devoid of *mature collagen fibrils in interstitial tissue*

Such lungs are incapable of expansion and contraction and therefore produce the symptoms mentioned It may afford some consolation to parents of children with this

that in many or most instances capillary leakage and the stasis of plasma in the alveoli and bronchioles rather than alveolar collapse explain the observed phenomenon Alveolar collapse alone does not predispose to the development of pneumonia but the stasis of plasma does —Ed]

Effects of Supine Position on Ventilation of Lungs of Dogs Cecil K Drinker and Esther Hardenbergh[4] (Harvard School of Pub Health) studied these effects by observing distribution of T 1824[*] aerosol introduced into lungs of anesthetized dogs in prone position After each experiment the animals were killed and the lungs removed without permitting collapse The aerosol imparted a blue color to the alveoli it entered Figures 22 and 23 show its distribution

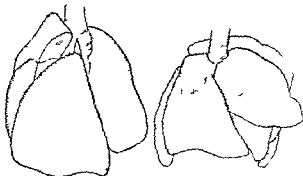


Fig 2 [illegible] — [illegible] T 18 48 [illegible] 50 m [illegible] 3 hou[illegible] [illegible]
Fig 3 (right) — [illegible]
(C[illegible] D[illegible] H[illegible] E[illegible] S[illegible] 4 113 118 [illegible] 1948)

Under anesthesia pulmonary blood flow is only sufficient to achieve adequate oxygenation of the blood There is settling of the blood to dependent parts of the lungs The authors believe that this settling coupled with little movement of the alveoli overfills the capillaries and after a time there is blockage of flow with leakage of a small amount of plasma into the alveoli and

(4) S[illegible] y 4 113 118 [illegible] 1948

signifying complete or nearly complete collapse of one or more pulmonary segments

Compression is not regarded as the sole cause for atelectasis to develop during deep narcosis In this state the lungs are reduced in volume to a degree commensurate with the extreme expiration The processes which keep air passages patent are interfered with and mucus accumulate The partial collapse of the lung interferes with collateral exchange of air between adjacent lung lobules through interalveolar ostia so that absorption of air by blood exceeds its entry into blocked alveoli from adjacent normal alveoli Possibly anoxia increases the amount of fluid in the small airways thus contributing to their obstruction Anoxia may also depress respiration

Besides usual methods for preventing atelectasis re-expansion of lungs and aeration of collapsed alveoli were attempted by holding the patient in a vertical position for 5 10 minutes this was *repeated every 30-60 minute* In comatose patients a fairly satisfactory tidal air and adequate pulmonary ventilation can be obtained by the Eve tilt method of artificial respiration These are only temporary expedients useful when mechanisms producing collapse will be dissipated or lessened in a few hours Breathing of 100 per cent oxygen periodically or continuously increased the depth of respiration even when carbon dioxide was not included nor allowed to accumulate in the mixture There was no increase in ventilation when carbon dioxide was added Intravenous glucose solutions were occasionally helpful in lightening narcosis and increasing depth of breathing The varying degrees of cyanosis observed were improved by these measure

The fever which was noted was probably not due to infection It is suggested that failure of heat loss through the lungs because of hypoventilation and from the skin because of peripheral vascular insufficiency was important in fever production

[This and the following article should be considered together The term atelectasis usually does not adequately describe the changes observed Circulatory changes such as those suggested by Drinker and Hardenbergh are of great importance 1

Etiology of Pulmonary Hemorrhage in Cats Exposed to Abrupt Deceleration Using a strain gauge pressure recorder Roger K McDonald Vincent C Kelley and Robert Kaye[6] (M C A U S) found that the aver age intra abdominal pressures in cats during deceleration was 1 657 mm Hg The decelerative force used was about that to which a man is exposed when traveling at 100 miles/hr and coming to a complete stop in 1 ft Pulmonary hemorrhage which follows abrupt decelera tion in the animals results from transmission of intra abdominal pressure to the lungs Removal of abdominal viscera before deceleration causes a remarkable decrease of pulmonary hemorrhage Application of a counter pressure device such as a narrow pressure cuff around the upper abdomen achieved similar results

Intra abdominal pressure was transmitted to the lungs by pressure waves which traversed the diaphragm The role of intravascular pressure transmission has not been evaluated completely Ultimate explanation of pulmo nary hemorrhage may lie in the differences between extra vascular and intravascular pressures Actual tearing of the pulmonary parenchyma was rarely observed Hemor rhage was primarily intra alveolar and did not follow a particular pattern Amount of hemorrhage seemed to vary inversely with distance of lung tissue from the diaphragm

Effect of Normal Saline Solution Ringer s Lactate Solution and Distilled Water on Lungs of Dogs and Rab bits In four dogs killed one hour after introduction of normal saline into their lungs Herbert C Miller Tom R Hamilton George W Wise and Herbert A Wenner[7] (Univ of Kansas) noted rare polymorphonuclear leuko cytes in the bronchi or alveoli minimal congestion and no pink staining material or hemorrhage in the alveoli Lungs of 19 dogs killed after six to seven hours had polymorphonuclear leukocytes in the bronchi and alveoli pink staining material in the alveoli and occasional

( ) J A t M 1 19 138 145 J 1948
(7) Am J P th 5 53 2 4 M h 1949

possible eventual blockage of bronchioles Thus is explained the reddish solidity of the dependent parts and absence of aerosol in them In prolonged anesthesia atelectasis slowly develops Stasis with subsequent alveolar collapse may be localized to the sternal margins of the lungs if anesthetized dogs are placed prone instead of supine

It is concluded that in every case of prolonged anesthesia or immobility in a single position the animal or man so treated must dispose of an abnormal pulmonary condition before normal health is attained

Papilledema in Emphysema Thomas Simpson (Enfield England) describes three cases of papilledema in emphysema and suggests their mechanism Bilateral papilledema is generally associated with and attributed to raised cerebrospinal fluid pressure in the cranial cavity In two patients cerebrospinal fluid pressure was elevated

The elevated spinal fluid pressure cannot be ascribed to elevated venous pressure for in the three patients the venous pressure was normal or nearly so Cases with high spinal fluid pressure and no papilledema differ from those with emphysema elevated spinal fluid pressure and papilledema in that the venous pressure of the former is generally elevated while that of the latter is usually normal

Simpson believes the cause of papilledema lies in the essential functional disturbance of emphysema the deficient hemorespiratory exchange In this condition oxygen saturation of arterial blood is low and its carbon dioxide content high Experimental and clinical observations suggest that this may produce enough cerebral vessel dilatation to raise the spinal fluid pressures above the level producing papilledema Although polycythemia may be a contributory factor in some cases it played no part in these cases

[This is an interesting clinical observation which should lead to further study It would be possible to determine accurately the frequency of the relationship suggested by Simpson —Ed.]

(5) Brit M J 2 639 641 Oct 7 1938

at the bedside without discomfort of arterial puncture or difficulties of gas analysis

METHOD —The oximeter consists of an earpiece and a galvanometer The earpiece fits over the pinna with an electric bulb in front and light filters and a photoelectric cell behind Heat generated by the bulb dilates arterioles of the ear and increases blood flow so that its oxygen content is equal to that of arterial blood Light from the bulb penetrates the ear and strikes the photoelectric cell in variable amounts depending on the quantity of oxyhemoglobin within blood vessels Record are made continuously by the galvanometer By comparison with results of many simultaneous arterial puncture Millikan ha shown that the instrument i accurate within 3 7 per cent A subject s oximeter response i the rise in galvanometer reading when he changes from breathing room air to 90 97 per cent oxygen in a B L B ma k A normal oximeter response is a ri e of 5 per cent or less a ri e of over 5 per cent indi cates anoxemia

When 10 normal subjects breathed 90 97 per cent oxygen from a B L B mask maximal oximeter response was 2 5 per cent Of 12 patients with acute cardiac infarction 9 showed increased oximeter responses some *as high* as *13 per cent The most obvious factors respon* sible for anoxemia in these subjects were pulmonary congestion in six and shock in three Anoxemia without demonstrable signs of shock or more than a few rales at lung bases was found in four patients In these there was no means of predicting oximeter response

Of 10 patients with congestive failure due to valvular disease old myocardial infarction or hypertension 5 had oximeter responses from 10 to 20 per cent and 4 from 6 to 10 per cent 1 had a normal response Although all whose response was over 10 per cent were moderately to markedly cyanotic before being given oxygen others equally cyanotic did not respond in this manner There was no clinical criterion which aided in reliable prediction of the degree of response

Figure 24 shows the responses of eight patients with pulmonary disease Of four with responses under 10 per cent three had emphysema and one extensive bilateral silicosis All of four patients with responses of 10 per cent or more had cyanosis orthopnea and tachypnea

hemorrhagic areas. Capillary congestion sometimes was pronounced but did not appear related to the number of polymorphonuclear leukocytes.

The least cellular exudate appeared in dogs given only local anesthesia with procaine, while the greatest amount was seen consistently in animals given pentobarbital sodium and morphine combined. The type of solution introduced into the lungs apparently did not affect the degree of polymorphonuclear response. Results of lung cultures and cell responses did not appear related. The polymorphonuclear reaction was diminished in animals killed 17-72 hours after introduction of saline solution compared with those examined after 6 hours.

Lungs of rabbits given normal saline solution intratracheally rarely had polymorphonuclear cells in the alveoli or bronchi. No explanation for the difference observed between the species can be given. Intratracheal injections of virulent pneumococci into rabbits has resulted in almost complete failure to produce lobar pneumonia, while in dogs it has met with a high degree of success. The dog's lung appears to be more nearly like that of man in its response to virulent pneumococci, suggesting that human lungs would react in a similar fashion to saline solution, water and Ringer's lactate solution.

[These observations should be considered in connection with the practice of irrigating the lungs for diagnostic or therapeutic purposes.—Ed.]

STUDIES OF DIAGNOSIS AND TREATMENT

Millikan Oximeter in Recognition and Treatment of Anoxemia in Clinical Medicine. Lincoln Godfrey, Harold S. Pond and Francis C. Wood[8] (Univ. of Pennsylvania) have found the oximeter useful in clinical management since it affords a simple, accurate, convenient and rapid method for assessing results of oxygen therapy

(8) Am. J. M. Sc. 16:60-618, December 1948.

pitalized four times in 11 months for congestive heart failure The fifth time he had anasarca orthopnea and cyanosis Oximeter response was 45 per cent with 90 97 per cent oxygen proved accurate by comparison with arterial oxygen saturation determinations The oximeter response showed that as little as 35 per cent oxygen in the inspired air would maintain a 30 35 per cent rise in oximeter reading Continuou oxygen by nasal catheter and digitalization were maintained diuretics were discontinued and fluid intake was not restricted Striking improvement followed and in three weeks he was discharged free from edema and from dyspnea when walking slowly In the ensuing 11 months he had led a quiet ambulatory life at home remaining free from congestive heart failure by using oxygen by nasal catheter at night and stopping it during the day Digitalis was continued

Oximeter response significantly above normal indicates anoxemia but a normal response does not rule it out Diagnosis of the condition underlying anoxemia may indicate the probable response to oxygen since in this series patients with cardiac infarction showed the smallest oximeter response those with congestive failure a small to moderate response those with pulmonary disease varying response and those with combined pulmonary and cardiac disease striking responses A small or normal oximeter response does not necessarily signify that oxygen therapy is useless if other indications for it exist Although cyanosis and pulmonary edema were usually associated with a significant increase in oximeter response no other signs proved reliable for purposes of prediction

Chronic Lung Failure According to J D Adamson[9] (Univ of Manitoba) chronic lung failure is a degenerative disease whose prime causes are emphysema and fibrosis Emphysema is due to loss of elasticity of the lung tissue As elasticity progressively deteriorates recoil of the lung becomes less vigorous and less complete The residual air after full expiration is much increased vital capacity is reduced and the lung is unable to retract from the position of inspiration because of loss of elasticity Every inflammation and irritation of

(9) P tg d M d 4 17 3 S pt ml 1948

causes were severe emphysema and bilateral broncho pneumonia spontaneous pneumothorax with 30 per cent collapse of the right lung complicating a chronic lesion (either congenital cystic disease or bronchiectasis) at the right base lobar pneumonia with secondary atelectasis and pleural effusion and extensive bronchogenic carcinoma All of six patients with combined pulmonary and

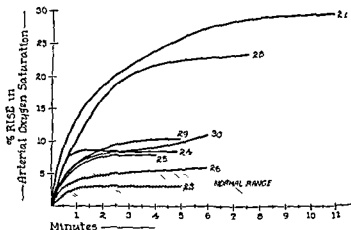


Fig 4—O m t r e p ses n p lmon y d (C t y of Godf y L et l Am J M S 216 605 618 December 1948)

cardiac disease showed definitely increased oximeter responses

Although in general the largest oximeter responses were obtained with the highest concentrations of inspired oxygen certain patients showed striking responses to lower concentrations Thus in selected cases the relatively low inspired oxygen concentration obtainable in an oxygen tent or by nasal catheter may be therapeutically effective Selection of such cases on clinical grounds alone does not seem possible The usefulness of the device is demonstrated in the following case in which accurate determination of oxygen need helped in instituting lifesaving therapy

Man 44 with advanced pulmonary fibrosis l w hos

pitalized four times in 11 months for congestive heart failure The fifth time he had anasarca orthopnea and cyanosis Oximeter response was 45 per cent with 90 97 per cent oxygen proved accurate by comparison with arterial oxygen saturation determinations The oximeter response showed that as little as 35 per cent oxygen in the inspired air would maintain a 30 35 per cent rise in oximeter reading Continuous oxygen by nasal catheter and digitalization were maintained diuretics were discontinued and fluid intake was not restricted Striking improvement followed and in three weeks he was discharged free from edema and from dyspnea when walking slowly In the ensuing 11 months he had led a quiet ambulatory life at home remaining free from congestive heart failure by using oxygen by nasal catheter at night and stopping it during the day Digitalis was continued

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(9) [illegible] 4 17 3 S[illegible]pt[illegible]mb[illegible] 1948

the lung initiates fibrosis With the passage of years vital tissues are replaced by fibrous tissue The effect of fibrosis is to make the lung smaller and interfere with expansion The signs of emphysema and fibrosis may cancel each other but usually one dominates the picture Emphysema may be primary or secondary to chronic infection or asthma

*The symptoms and signs of emphysema are easily rec*ognized when they are far advanced the barrel shaped chest fixed in a position of almost full inspiration the insistent paroxysmal cough the severe dyspnea on effort

POINTS DIFFERENTIATING DYSPNEA OF EMPHYSEMA FROM CARDIAC DYSPNEA

DYSPNEA OF EMPHYSEMA	CARDIAC DYSPNEA
Very gradual onset (5 10 years)	More sudden onset (months)
Always worse in winter and cold air	Not necessarily
Usually normal respiratory rate	Tachypnea common
Obvious expiratory difficulty	No special expiratory effort
Dyspnea apparent to observer	May be inconspicuous
Not very distressing	Usually accompanied by anxiety or fear
Not paroxysmal or unprovoked (unless asthmatic)	Spontaneous nocturnal attacks
No obvious cardiovascular signs	Other objective signs of cardiovascular disease

the recurrent attacks of bronchitis bronchospasm or pneumonitis and finally right heart failure Dyspnea is the cardinal symptom and emphysema cannot be diagnosed in its absence The table lists a few points which may aid in differentiating dyspnea of emphysema from cardiac dyspnea Cough appears with the dyspnea or soon afterward It is spasmodic and paroxysmal and each is prolonged and gusty It may be brought on by effort cold air dust or laughter Expectoration is always scanty or absent for a long period in primary emphysema Weight loss and easy fatigability may be present ing symptoms

Since the fundamental defect is loss of ela [illegible] the

most dependable sign is reduction in movement of the thorax This can be tested by standing behind the patient and placing the fingers in the intercostal spaces In emphysema the sensation of vigorous inflation disappears and the thorax seems paralyzed at the top of inspiration This test is more useful in diagnosis than x rays or vital capacity estimations Another important physical change is increase in thoracic index (anterior posterior diameter/lateral diameter) As emphysema increases the chest becomes deeper and any figure over 0 75 almost certainly means emphysema General undernourishment varying degrees of cyanosis hyperresonance to percussion weak breath sounds prolonged expirations rhonchi and myotatic irritability may also be found

Progress of chronic lung failure may be retarded if recognized early by taking precautions against wear and tear on the lungs Wider use of antibiotics and similar drugs in subacute and chronic pulmonary inflammations would help prevent lung failure Hard manual labor *should be avoided The amount of useless cough*ing should be reduced The patient with cough should be thoroughly examined and the primary cause appropriately treated Anyone with an otherwise unexplained cough should immediately give up cigarets It may require several weeks abstinence to show the usual striking results

[These are interesting and helpful interpretations for the clinician Frequently the pulmonary fibrosis diagnosed by the clinician usually on the basis of x ray findings is not found at autopsy and the symptoms were due to emphysema alone Although as Adamson states repeated and chronic infections may lead to fibrosis it should be emphasized that chronic bronchitis alone may aggravate the symptoms of emphysema because of interference with pulmonary ventilation His point is well taken that heavy physical labor should be avoided such effort probably accounts for the more frequent occurrence of severe emphysema among men as compared with women Also the advice to give up smoking is rational since this may diminish greatly the bronchitis and bronchorrhea which add to the difficulty —Ed]

Mediastinitis Anterior Chronica A J M Lohman[1] studied five patients with precordial complaints attributed

(1) Acta med Scand 131 51 65 1948

to chronic inflammation of the anterior mediastinum between the visceral pericardium and the posterior surface of the sternum and xiphoid process Mediastinitis was

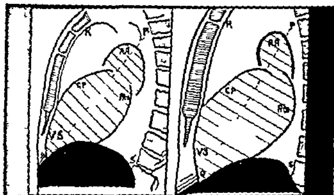




Fig 5 (ft) — S gtt l film s o m l m n
Fig 6 (ght) — S gittal film of n al w ma
(Cou t sy f Loh n A J M Act m d S nd nav 131 51 65 1948)

thought to have resulted from streptococcic or influenzal infections secondary to bronchitis

History in this condition is characteristic Illness begins acutely with symptoms of influenza accompanied by coughing high fever and oppression of the middle of the

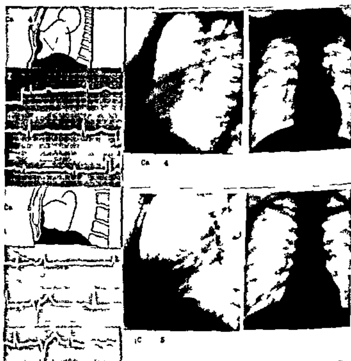
chest Acute symptoms soon disappear but subsequently the patient complains of nonradiating oppressive pain behind the sternum accentuated by exercise After some months fibrosi causes inward retraction of the xiphoid process to form a pseudofunnel chest which can be distinguished from the congenital or rachitic funnel chest in which the whole sternum is inclined inwardly Of Lohman s five patients three thought they had heart disease

In these patients anteroposterior x rays of the chest and electrocardiograms (except in one patient) were normal Lohman has found sagittal chest x rays to be of most value in diagnosis Sagittal x rays of a normal man and a normal woman are shown in Figures 25 and 26 The normal findings of most value are clear anterior diaphragmatic sinus seen as a 90 degree angle between the posterior surface of the sternum and xiphoid process and the thoracic surface of the diaphragm normal alinement *of the xiphoid process triangular space formed by* the right atrium front of the spinal column and diaphragm and the fact that the axis of the heart (*VS AA*) forms the diagonal of the quadrangle *PQRS*

CASE 4—Woman 37 had had increasing pain and oppression in the middle of the chest since an acute illness accompanied by violent coughing three years previously Blood pressure was 145/90 and heart sounds were normal Sedimentation rate and tuberculin and Wassermann tests were negative Typical pseudofunnel chest was present Sagittal x ray of the thorax showed thickening of precordial tissue heart axis at a 30 degree angle to the diaphragm conversion into a slit of the usual triangular space formed by the right auricle spine and diaphragm the front of the heart adherent and the anterior diaphragmatic sinus obliterated by elevation of the diaphragm toward the xiphoid process (Fig 27) Electrocardiogram showed no significant change

CASE 5—Woman 53 complained of nonradiating pain in the middle of the chest for more than six months Blood pressure was 160/100 Extra systoles were detected clinically and on the electrocardiogram Heart sound were muffled but otherwi e normal and an early funnel chest was found Sedimentation rate and Wassermann te ts were normal and tuberculin positive Sagittal x ray showed the xiphoid

process pointing backward the heart axis forming a right angle with the diaphragm the front of the heart adherent to the sternum and the shadow of the mediastinum behind the sternum thickened just above the diaphragm (Fig 28) There



F g 2 (t p) – S g tt l film h w g th ke g beh d rl d p oce d l ft ng f nt o d ph gm t c n A t po t film h w n m l d l ct d g m n t w thy ch g
F g 28 (bott m) —S g ttal film h w g th k g beh d x ph id p o a d l ft g f ant o d aph gm t c n A t opo t o film h w no anomal e d elect o a d g am h ws me nt c l t a y t !
(C u te y of Lohm n A J M Act m d S d n 131 51 65 1943)

were some widening of the P wave notching of QRS complex and deviation of S T segment and ventricular extrasystole

Operative repair of the deformed sternum and xiphoid process was carried out on one of the five patients The anterior mediastinum was found to be filled with tough connective tissue 1 5 cm thick

[This conception needs further study and elucidation in order to diagnose anterior mediastinitis more accurately. It is necessary for instance to distinguish mediastinal pleurisy which may have some of the same features although the chronic inflammation is outside the mediastinum. Retrosternal oppression and pain may be observed in patients with various chronic pulmonary lesions; silicosis is one example.—Ed.]

Clinical Significance of Pulmonary Hemorrhage. Study of 1,316 Patients with Chest Disease. In the groups studied by Osler A. Abbott (Emory Univ.) 497 (38 per cent) gave a history of bleeding from the lung but type of hemoptysis and underlying disease could not be correlated. Hemoptysis producing lesions were no more frequent in one lung than the other or in any individual lobe. The primary symptom was cough in 62 per cent and hemoptysis was noted in 21 per cent. Bleeding is usually a late occurrence in the sequence of symptoms in bronchogenic carcinoma.

Bleeding occurred in 53.6 per cent of patients with bronchogenic carcinoma, 49 per cent with lung abscess, 44 per cent with pulmonary infarct, 45 per cent with bronchiectasis and 36.5 per cent with tuberculosis. It is of interest that bleeding occurred in 5 of 24 patients with metastatic carcinoma. Hemoptysis may occur when aortic aneurysms erode an adjacent bronchus. It does not necessarily denote primary lung disease but may be caused by mediastinal tumors, pulmonary hypertension secondary to mitral stenosis or congenital heart disease.

In patients suspected of acute lobar or bronchopneumonia, hemoptysis lasting more than 48 hours, not of classic "prune juice" type but containing small amounts of little clots or streaking, should be considered atypical and intensive investigation should be made to rule out obstructive, ulcerative or compressing lesions of the bronchial tree. Abbott has found subjective localization of bleeding site by the patient highly effective. Careful history taking and physical examination, x-ray, bronchography and bronchoscopy, sputum and biopsy studies as well as intelligent use of exploratory thoracotomy lead to earlier recognition and more successful treatment.

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Bacteriologic Examination of Tissues Surgically Removed as Aid in Diagnosis of Diseases of Chest Herman J Moersch L A Weed and John R McDonald[3] (Mayo Clinic) state that recent progress in treatment of pulmonary disease by chemical antibiotic and surgical means makes it desirable to determine underlying etiology so that the most satisfactory treatment can be used The importance of establishing early a positive diagnosis is manifest when it is realized that lung cancer and tuberculosis may mimic practically any type of pulmonary disease For indeterminate lesions exploratory thoracotomy is often advisable and will frequently reveal unexpected and significant abnormality In all cases close co operation of roentgenologist bronchoscopist bacteriologist pathologist and other specialists in study of the patient and examination of biopsy and surgical material is highly important for accurate diagnosis

This point of view is given weight by results in three cases of Coccidioides immitis infection one of Aspergillus fumigatus infection one of Histoplasma capsulatum infection and one of infection due to pasteurella of the animal variety In each diagnosis was possible because of co operation of the various specialists

[This suggestion is very pertinent and might well be followed whenever resections of lung tissue are performed —Ed]

TUBERCULOSIS

Study of Tuberculosis Mortality in England and Wales According to Percy Stocks[4] (Gen l Register Office) before World War I the United States had a higher tuberculosis mortality rate than England and Wales a steep fall brought the rates close together in 1920 and since 1921 the United States has shown a large advantage In England and Wales percentage reduction in mortality was constant between 1875 and 1910 and after

(3) D f Ch t 15 1 5 140 F b ry 1949
(4) T be cle 30 50 61 M ch 1949

recovery from World War I the downward trend be came slightly steeper After the second setback early in World War II the rates were again below values ex pected if the steady fall before 1910 had continued with out change The rate of improvement of the compara tive mortality index during the last 10 years has been considerably less than that in any 10 year period between 1871 and 1935 Crude death rate in 1936 37 was 567/mil lion whereas in 1947 it was 468 The over all trend from 1938 39 to 1946-47 showed an 11 per cent fall in crude rate at all ages and a 7½ per cent fall in comparative mortality index

For children under 5 with respiratory tuberculosis the 1946-47 level was about 40 per cent above that of 1938 39 whereas had the prewar trend continued it would have been about 50 per cent below For boys 5 10 the rate increased greatly in 1940 41 and although it is again falling it has not regained the best prewar level For girls of this age mortality did not substantially in crease but the prewar downward trend has been arrested Among children 10 15 present mortality is well below that of 1938 39

Among young adults 15 45 rates were declining rap idly before the war the fall was broken in 1940 41 but was resumed by 1942 43 and has continued since then for most sex and age groups though more slowly than in the prewar years Mortality rate of women between 45 and 65 was only slightly raised in 1940 41 and the downward trend was quickly resumed improvement since 1938 39 being by about one fifth Among men 45 55 the rate has fallen 10 per cent since 1938 39 but at 55 75 rates are now hi her than they were even in 1931 35 and show no sign of improving This may be explained by the fact that men who are now 55 80 bore the brunt of World War I and many of the fittest were killed and in World War II the group was again subjected to heavy strains Since 1938 peak male death rate has been at ages 55 65 whereas for females it has been from 20 to 2-

On the average a death from tuberculosis robs the community of 24 years of future working life between ages 15 and 65 whereas cancer causes a loss of only 5 years and a fatal accident 18 years between those ages

[Stocks's conclusions based on a statistical approach are of great interest in connection with those set down by Medlar and his associates (p 183) on the basis of pathologic studies A comparison of statistics (*Tuberculosis Reference Statistical Year Book* New York Tuberculosis and Health Association 1948) for New York City in 1947 shows a death rate from tuberculosis among men above 50 varying from 114 to 146 per 100 000 compared with a death rate among males from all types of cancer of 201 It is also of interest that the death rate from cancer of the lung among males was *21 8 (4 7 among females)* —Ed]

Reproduction of Human Ulcerative Pulmonary Tuberculosis in Rabbits by Quantitative Natural Air Borne Contagion Using a modified Wells apparatus for quantitative air borne infection Max B Lurie and Samuel Abramson[5] (Univ of Pennsylvania) exposed 29 rabbits of unknown genetic resistance to tuberculosis to inhalation of varying numbers of highly virulent bovine tubercle bacilli of Ravenel strain grown on modified Lowenstein medium There were 5 to more than 1 200 bacillary units/liter of air respired by the rabbits in individual experiments The rabbits were killed five to six weeks after exposure and the number of primary tubercles in the lungs carefully determined In general the larger the number of bacilli inhaled the larger the number of primary pulmonary foci There was no constant ratio between the number of bacilli required to generate a single tubercle Average ratio in all animals was 9 ± 7 bacillary units/tubercle generated Whether this ratio depends on native resistance of rabbits or on other factors has not been determined

Five highly inbred genetically resistant rabbits of the same family were given six consecutive weekly intracutaneous injections of heat killed bovine type tubercle bacilli totaling 7 mg/rabbit These animals and a sixth unvaccinated animal of the same race were exposed simultaneously in the apparatus for 10 minutes to

(5) Proc Soc Exp Biol & Med 69 531 537

droplet nuclei of virulent bovine type tubercle bacilli of Ravenel strain 5½ months after the last injection There were 10 bacillary units/liter in the air respired by these rabbits Subsequent studies showed all the degrees of resistance seen in man from failure of the disease to take root at all to formation of primary lesions which did not extend beyond the site of inception to limited bronchogenic dissemination from primary ulcerative foci to unilateral ulcerative tuberculosis and finally to rapidly progressive ulcerative tuberculosis which had destroyed one lung and was progressing from upper to lower lobes in contralateral lung There was little or no lymphogenous or hematogenous dissemination but the animals varied decidedly in ability to restrict dissemination of disease by bronchogenic spread

[The question naturally suggests itself what become of inhaled bacilli which do not produce tuberculous lesion The assumption is that the body defense may be able to cope with and destroy them This technic of producing relatively chronic disease in animal will be a useful experimental tool —Ed]

Disregarded Seedbed of Tubercle Bacillus To determine the location and extent of the unknown source of infection Edgar M Medlar David M Spain and Robert W Holliday[6] (Bellevue Hosp New York City) studied the 1935-44 autopsy records of adults over age 15 Caseous foci without cavity formation in the lungs were seen in 2 per cent of all autopsies Such foci are areas of necrotic tuberculous pneumonia and precursors to cavity formation Until completely organized they are a potential source for discharge of tubercle bacilli into the air Of patients with this type one third were under 50 of whom 54 per cent died of tuberculosis two third were over 50 with death from tuberculosis occurring in only 19 per cent Among Negroes 9 per cent had this type of focus 77 per cent being under 50 and death from tuberculosis occurring in 94 per cent Of white patients one sixth had this type 72 per cent being over 50 and death from tuberculosis occurring in only 18 per cent Apparently caseous foci show a greater tendency to

6 Arch Int Med 81 501 517 Apr 1 1948

soften and excavate in Negroes than in whites a possible reason for the difference in behavior of the disease in the two races These caseous foci have not received the attention they merit for clinical diagnosis of tuberculosis was made in only 25 per cent

In 40 per cent of persons with unhealed pulmonary tuberculosis over age 50 this disease was not mentioned in the clinical diagnosis Of this group 77 per cent were white males of whom half had cavity formation in the lungs Tuberculosis acquired later in life tends to be less explosive and manifestations may be so few that patients do not seek a physician s advice In the majority clinical recognition of tuberculosis would not have altered the primary diagnosis or treatment but failure to recognize active tuberculosis permitted the patients to be unrecognized spreaders of infection

When all persons who died of tuberculosis and all with a clinical diagnosis of tuberculosis are excluded from the autopsy series there remain 183 (2 5 per cent) with unhealed disease 40 per cent of whom had cavity formation This represents a rate of 1 000 persons with unrecognized cavity formation in the lungs/100 000 of the population With so many unrecognized spreaders of bacilli exposure could occur often and new cases develop without discernible source of contact

Control of tuberculosis meaning decrease of continuity of the disease rather than decrease of mortality rate requires planned follow up of all persons with unhealed disease including those with x ray shadows regardless of whether the disease is considered active or inactive Socioeconomic factors that favor tuberculosis must also be olved by intelligent action The search for unknown spreaders of infection must be intensified and those with active tuberculosis must receive adequate hospitalization In addition search for a cure in a pathologic as well as in a clinical sense must be intensified

[This study demonstrates the reservoir of tuberculosis among elderly men In New York City the death rate above age 50 from this cause is four to five times as high among men as among women furthermore there has been little or no r in the

death rate from tuberculosis among elderly men in the last 10 or 15 years —Ed]

Age Variation of Incidence of Tuberculosis O M Andenaes[7] reports on a tuberculin survey using the Pirquet and Mantoux tests in the health district of Kyrkjebø in 1939-40 Of 1 260 negative reactors retested in 1946-47 180 gave a positive response Annual incidence of infection for the district was 2 5 per cent and was higher in the town of Høvanger (3 per cent) than in the surrounding rural area (1 3 per cent) The tuberculin conversion incidence as elsewhere in Norway was higher in males (3 1 per cent) than in females (1 7 per cent) From 1 6 per cent in childhood it increased to 3 4 per cent in early adult life but returned to childhood values in more mature age Under such conditions primary infections may occur at all ages and the percentage of infection in separate groups of the population never reaches 100

This age variation of infection frequency is perhaps accidental but may be characteristic of the epidemiologic state of the district Investigators elsewhere should discover whether this phenomenon also occurs in other areas

The low infection rate of children is usually attributed to sheltered life within the family The fact that pulmonary tuberculosis does not develop in children and therefore they do not infect their playmates may be a still more decisive factor The sudden rise of infection risk from childhood to early adult life is usually attributed to adolescents leaving home to enter the workshops Work time is however only eight hours and off time is perhaps more dangerous than working hours Adolescence is characterized by extensive and intensive friendships with intimate associations in sport play and flirting These associations are all the more dangerous because in these years highly infectious pulmonary lesions frequently appear When the individual has married and adopted the more sedate life of middle age the circle of

(7) A d m d. 39 1679 1948

friends shrinks and infections become rare If the ri e of infection rate seen in adolescents characterizes not the whole adult age period but only its early years the chances of prophylaxis against primary infection become promisin

Relation of Economic Status to Tuberculosis Mortality by Age and Sex Milton Terris[8] studied the incidence of tuberculosis mortality by age sex and economic status in Buffalo for 1939-41 The population was divided into four quarters using median monthly rent proportion of homes with central heating proportion of homes with mechanical refrigeration and median years of school completed as the indexes of economic status Each quarter included about 145 000 people

Death rate after the third decade was significantly higher for both white and nonwhite males Below age 35 tuberculosis mortality for both males and females in the lowest economic quarter was about double that in the highest quarter In females aged 35 and over mortality in the lowest quarter was a little more than double that in the highest quarter For males aged 35 and over mortality in the lowest economic quarter was almost four times as great as in the hi hest quarter Mortality differences between the highest and lowest economic quarters were statistically significant for all groups

These data indicate that the high male mortality after age 35 is not merely a matter of economic status per se If it were females in the lower economic groups should show a similar rise in mortality after age 35 It is suggested that physical overstrain associated with occupation plays an important role in the disproportionately high tuberculosis mortality among adult males in the lower income group

[The role of nonspecific factors in resistance against tuberculosis is important Some of these are constitutional and others environmental A steady improvement of the latter helps to explain the fact that the United States has the lowest death rate from tuberculosis in the world —Ed]

(8) Am J Pub H alth 38 1061 1070 A g t 1948

Protective Vaccination against Tuberculosis with Special Reference to BCG Vaccination is reviewed by Joseph D Aronson[9] (Univ of Pennsylvania) Tubercle bacillus was identified as the specific organism of tuberculosis by Koch in 1882 Soon after this it was found that animals once infected with tubercle bacilli resist reinfection Koch s discovery of tuberculin in 1890 raised hopes that the attenuated tubercle bacillus might have protective value against tuberculosis It was not until 1921 however that a safe attenuated tubercle bacillus was produced After 230 transplantations of a strain of tubercle bacilli on potato medium during a 13 year period Calmette and Guerin produced an attenuated strain (BCG) which has been used widely in Europe South America and Japan

In 1935 the United States Department of the Interior fostered use of BCG for prevention of tuberculosis among Indians in Alaska Arizona Wyoming and North and South Dakota BCG was given intracutaneously to 1 551 Indians aged 1 20 and to 123 newborn infants Simultaneously 1 457 Indians of comparable age and living conditions were given intracutaneous injections of sterile physiologic saline and served as controls along with 139 newborn infants

No untoward local or general reactions followed injection of vaccine Vaccinated and control person were followed 9 11 years by tuberculin tests and chest x rays and infants were observed 6 8 years Mortality rate from all causes was 3 1/1 000 person years of observation for the vaccinated and 7 2 for controls Among 1 551 vaccinated there were 55 deaths 6 from tuberculosi among 1 457 controls there were 109 deaths 53 from tuberculosis The mortality rate for tuberculosis per 1 000 person years of observation was 0 4 for the vaccinated and 3 5 for the controls Among 123 newborn infants vaccinated and observed six to eight years 7 died none from tuberculosis Among 139 control infants followed

(9) Am R T b 58 55 81 S p ml 1948

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(8) Am J P b H lth 38 1061 10 0 Aug t 1948

in except those for employees of two mining companies which were 14 × 17 in In this manner 97 8 per cent of the population was examined In a follow up survey of the same type in 1946 89 6 per cent wa examined In none of the persons with normal chest x rays in the first survey did pulmonary tuberculosis develop in the sub sequent three year period Of 149 persons found in the first survey to have inactive tuberculosis 108 showed no significant change in the second survey The other 41 patients with inactive tuberculosis were not re examined in 1946 15 had recent satisfactory chest x rays 11 had moved from the community and were not traced 9 were still living in the community but were un co operative 4 died of nontuberculous disease and 2 had reactivated dis ease The last two patients were hospitalized and one died of tuberculosis

Of 14 persons with active tuberculosis in 1943 8 were admitted to a sanatorium 1 was treated at home 1 died at home 3 left the county and 1 has not yet been admitted to a sanatorium In the 1946 survey six persons were classified as having active or suspiciously active tuberculosis Of these three showed suspicious evidence of active tuberculosis in 1943 which was not then recog nized as such One was not included in the first survey because he was away at the time and the other two were in military service in 1943 Of these six persons five have been admitted to a sanatorium admission of the sixth was not advised because activity of the lesion re mained questionable

To estimate effectiveness of the 1943 survey and treat ment instituted as a result of the survey the number of new cases of tuberculosis which actually developed in the three years between the two surveys was compared with the number that might have been anticipated had no survey been made It was estimated that during this period 12 cases could have been expected if there had been no change in population When this figure was cor rected for population changes there were an estimated 11 cases In contrast to this expected figure only one

15 died 4 from tuberculosis Tuberculin reaction was positive a year after vaccination in 93 3 per cent of subjects and remained at approximately the same level throughout the study Among controls tuberculin reaction was positive in 12 7 per cent within a year after initial negative reaction and there was a constant gradual increase in percentage of controls reacting to tuberculin Lesions of primary tuberculosis were detected by x ray in 22 vaccinated and 120 controls minimal lesions of reinfection type progressive lesions and miliary and extra pulmonary lesions were found in 21 vaccinated and 93 controls

[The most definite and impressive favorable effects of BCG vaccination are those reported among population groups in which there is an exceptionally high incidence of tuberculosis The Aronson study and that of Ferguson and Simes (Tubercle 30 5 11 January 1949) are examples It is of interest that the death rates among vaccinated subjects as reported by Aronson, were about the same as the rates prevailing throughout the United States where vaccination has been used on a very small scale and in only a few areas The implication seems to be that non specific resistance may be promoted with effects comparable to specific vaccination This of course does not argue against vaccination among highly exposed groups as advocated by Birkhaug (New York State J Med 49 401-406 Feb 15 1949) Although BCG has not been observed to be harmful it has mild virulence for guinea pigs and the desirability of a killed vaccine of equal efficacy is recognized Paterson Crombie and Coles (Canad J Research Sect. E 27 37-42 February 1949) have pursued this line using experimentally a vaccine made from vole bacilli killed by ultraviolet light. In guinea pigs they observed a degree of protection comparable to that obtained from BCG but it is not known whether the duration of protection from the killed bacilli would be as long as that conferred by BCG which seems to be several years at least —Ed]

Complete Community Survey for Tuberculosis Second Report on Effectiveness of Procedure as Method of Tuberculosis Control is presented by *Roberts Davies G A Hedberg, and Mario Fischer*[1] *In* 1943 a complete community examination of Ely Minn was made to detect pulmonary tuberculosis The town s 6000 persons were canvassed and all households were notified when to expect a mobile x ray unit in their area Persons who did not come for examination were called by a volunteer worker or public health nurse All films were 4 × 5

(1) Am R v T berc 58 77 84 J ly 1948

their contacts In 1939 the sanatorium teaching service was eliminated and medical students were taught tuberculosis in a general hospital with a chest disease service operated on a strict contagious disease basis

As a result of these efforts number of tuberculin reactors on graduation decreased from 77 9 per cent in 1936 to 50 4 per cent in 1941 and 37 4 per cent in 1945 In 1936 over 65 per cent of the nonreactors on entrance became reactors while in school When the control program was put into effect this percentage reached 20 in 1941 7 8 in 1945 and 3 2 in 1947 Reduction in incidence of *primary tuberculosis was accompanied by decrease in* number of lesions which became large enough to be located by physical and x ray examination of the chest This was true for those who had primary tuberculo is on entrance and those who contracted it while in school Since fewer students became primarily infected it is probable that a smaller number of reinfections occurred The question is raised as to whether exogenous reinfections are not more significant in causing clinical tuberculosis than had formerly been believed

In every person who contracts tuberculosis the disease can be diagnosed by the tuberculin reaction within eight weeks after the bacilli invade the tissues At this time chest x rays rarely reveal any evidence of the disease in more than 5 10 per cent of the cases A tuberculin reaction showing an area of edema or induration 5 mm or more in diameter is regarded as diagnostic of primary tuberculosis

Because of the simple method required to establish the diagnosis of contagious tuberculosis and the satisfactory contagious disease technics for protection of contacts of persons with active disease the authors do not believe in the unavoidable exposure concept

[Exp ence indicates that phys cians have almo t un formly acquired tuberculous inf ction usually before leaving med cal school and if n t then befo e le ing the h pital internship The des rability of p stpon g nfection is gen rally agreed on but in view of the nume ous contacts of a physician some favor the use of PCC vaccinati n among med cal tudents Preservation of good general he lth and livi g tandards pr bably expla ns the unu u

case developed during the three years The patient was a woman 46 previously in apparently good health who had tuberculous meningitis in 1945 and died after a short illness

The authors conclude that examination of a high percentage of population for pulmonary tuberculosis hospitalization of patients with active disease and follow up examinations of patients with inactive disease can be expected to result in a sharp drop in incidence of new cases of tuberculosis In the community studied most new cases of clinical tuberculosis occurring in recent years resulted from recent exogenous infection

[Such studies demonstrate the possibility of tuberculosis control. Obviously the problem is much more complex in large urban populations —Ed]

Prevention of Tuberculosis among Students of Medicine is discussed by Harold S Diehl Ruth E Boynton Susanna Geist Black and J Arthur Myers * At the University of Minnesota tuberculin testing plus chest x rays for reactors became a routine procedure for entering students in 1929 Reactors with shadows are given a complete examination to determine the cause of the lesions Nonreactors to tuberculin are retested annually as long as they do not react Those who become reactors while in school and those who were reactors on entrance are given annual chest x rays and complete examination when indicated These studies disclosed that approximately as many students contracted primary tuberculosis (tuberculous infection) during the brief time they were in school as had acquired this disease between birth and matriculation It was apparent that more students became infected on tuberculosis services than in general hospitals

By 1938 tuberculosis control programs among personnel and patients had been instituted at the two hospitals where most of the students worked Both employees and patients in whom contagious tuberculosis was revealed were immediately isolated and treated with strict contagious disease technic so as to protect all

* ( ) J A M A 138 8 11 S pt 4 1948

mask Conversely masks will not retain invisible droplet nuclei containing tubercle bacilli propelled through them by extremely forceful expiratory chest movements during fits of coughing

[It is hardly practical for human beings to wear masks like those applied to these rabbits nevertheless the study is scientifically valuable There should be further investigation to find a reasonably effective mask which would be practical Aside from this it should be remembered that patients may b educated to minimize cough thus avoiding heavy air contamination Good general hygiene should not be underestimated in preventing transmission of infection — Ed]

Pathogenesis of Minimal Pulmonary Tuberculosis Study of 1,225 Autopsies in Cases of Sudden and Unexpected Death In this 20 year study E M Medlar[4] (Columbia Univ) found 96 cases with caseous or calcific foci or both which in his opinion would have ca t some sort of x ray shadow In 42 7 per cent the disease was primary and in the remainder was of reinfection type Calcified primary complexes were twice as frequent in persons over 40 as in those under 40 the ratio being even greater in Negroes and males Primary lesions of minimal extent were 2 7 times more frequent in persons under 40 than in those over 40 the incidence again being greater in Negroes and males Reinfection lesions of minimal extent were found 10 times more often in persons over than in persons under 40 and over 80 per cent of these cases occurred in the white race especially in males Minimal lesions were primary in 91 per cent of persons under 40 and represented reinfection in 72 6 per cent of those over 40 Macroscopic tuberculous foci were observed in abdominal organs of 11 (26 8 per cent) in the primary group and 1 (3 6 per cent) in the reinfection group suggesting that extrapulmonary tuberculosis may occur more often in persons with primary than with reinfection disease

Primary and reinfection lesions could not be differentiated by their location Primary and reinfection groups contained lesions having similar characteristics although proportional distribution within age groups was consid

(4) Am Re T be 58 583 611 D mber 1 48

ally low death rate from tuberculosis among physicians de pite the high infection rate

Meade (Am Rev Tuberc 58 675 683 December 1948) reports the experience at the University of Rochester Medical School where the incidence of tuberculosis among students was reduced after they no longer handled specimens and other material in the pathology laboratory Although sensible precautions are to be fa vored these should not interfere with the students education There has been considerable feeling that mo t medical graduates are in adequately informed about tuberculosis —Ed.]

Efficiency of Gauze Masks in Protection of Rabbits against Inhalation of Droplet Nuclei of Tubercle Bacilli Rabbits without masks and rabbits wearing three and six layer gauze masks 40×44 threads/sq in sewn to fit contour of head neck and ears were exposed simul taneously by Max B Lurie and Samuel Abramson[3] (Univ of Pennsylvania) to air containing droplet nuclei of highly virulent bovine tubercle bacilli of Ravenel strain Some rabbits without masks were killed immedi ately after exposure and lung suspensions planted on modified Lowenstein medium Number of colonies de rived from a known weight of lung parenchyma indi cated total number of viable bacilli in both lungs The range was from 30 to over 1 000 and averaged 275 tu bercle bacilli units/rabbit Eighteen unmasked rabbits which lived four weeks had an average of 28 tubercles/ animal whereas 19 simultaneously exposed masked rab bits which lived the same length of time averaged 1 4 tubercles There were no grossly visible tubercles in 12 of the masked rabbits Efficiency of the mask in sup pressing grossly visible primary pulmonary tubercles was 95 per cent Number of layers of gauze in the mask did not influence final results

Masks were applied to rabbits so that all respired air passed through them To be equally effective for human beings exposed to air borne infection of tuberculosis masks must be worn in an equally effective manner Persons wearing masks should refrain from deep in spiration as much as possible as the forceful suction so produced may diminish the filtering efficiency of the

(3) Am Re Tube c 59 1 9 Jan a y 1949

cent under age 3 Negroes outnumbered whites 2 1 the proportion of boys to girls was about equal

Healed or healing primary complex was observed in 66 15 having extrapulmonary tuberculosis but no other pathologic changes in the lungs and 19 showing in addition miliary dissemination in the lungs and other parenchymatous organs Progressive primary complex was present in 23 all but 4 of whom were Negroes Children with this form exhibit progressive enlargement of the primary focus with liquefaction and cavity formation and extensive and advanced lymph node involvement Hematogenous tuberculosis in children results from dissemination in the blood stream after development of a primary complex (early abortive or progressive generalization) or from dissemination from an active extrapulmonary tuberculous process after the primary complex has healed (late generalization) In early abortive generalization disseminations cease and miliary foci undergo anatomic healing as soon as the primary complex is sealed off by encapsulation but size and number of hematogenous seedings depend on extent of the primary complex In the majority healing takes place with no further tuberculous activity In early progressive generalization the source of bacillemia undergoes progression and hematogenous disseminations continue until death All 23 children with progressive primary complex showed evidence of hematogenous dissemination and in addition to miliary foci most showed caseous foci up to 1 cm in diameter Late generalization occurred in six children The gross and microscopic pictures were those of acute generalized miliary tuberculosis similar to that seen in adults

Twenty children all with a healed primary complex in the lung had chronic pulmonary tuberculosis Ages varied from 18 months to 12 years and 60 per cent were Negro Presence of a calcified encapsulated primary complex is ample proof that the chronic disease did not develop from a primary focus The clinical course x rays and autopsy findings were similar to those of chronic

erably different In persons under 40 9 of 10 caseous lesions were primary but in persons over 40 10 of 13 caseous lesions were of reinfection type Only 23 foci (23 9 per cent) were caseous 13 were completely healed and the remainder showed some attempt at repair Only 7 9 per cent of lesions in upper portions of the lobes were healed whereas 42 8 per cent in lower halves were healed Parenchymal lesions had no macroscopic or histologic characteristics which distinguished primary from reinfection disease

There was no evidence that minimal tuberculosis arises as a prompt reaction to massive air borne infection or is either hematogenous or lymphohematogenous When minimal pulmonary tuberculosis is first demonstrable with x ray caseation of an area of tuberculous lobular pneumonia is present and local endobronchial metastasis has already occurred in a high percentage Lesions were predominantly dorsal in position and within the upper half of pulmonary lobes both apical and subapical They were unilateral in 82 per cent It is not understood why certain areas of lung parenchyma are subject to development of progressive disease but posture may have an influence

The distribution pattern of minimal lesions is important in mass chest x ray surveys Lesions may be located so that heavy structures of shoulder girdle and spinal muscles make their demonstration difficult Upper lung field lesions with scattered calcifications also contain areas of tuberculous pneumonia and should not be interpreted as healed

The data in this paper support the view that adults especially if young with disease of minimal extent should be given careful hospital supervision

[This study emphasizes the serious portent of minimal tuberculosis in young people Absence of symptoms and other indications of activity of the infection do not necessarily minimize the possibility of progressive disease if proper treatment is not given —Ed]

Tuberculosis in Children Oscar Auerbach[6] (Staten Island) studied 90 patients all under age 13 and 40 per

Am J D C 11 75 535 569 Ap 1 1948

29) Also cattered in the plenic pulp were ill defined areas of fibrinoid necrosis abounding with acid fast bacilli (Fig 30) The only other remarkable gross changes were kidney and spleen infarcts There was noticeable l ukopenia of the bone



Fig 29 (l ft) —\ t g d phl t (F \) pl t g n m ou t b l b ll (t h w) R d d f m × 50
Fig 30 (ght) —A f ec os pl h w g m s f d f t b ll p p ed by Z hl N l n m thod R d d f m × 535
(Courtesy f Tag l W d Woolf A L Am Re T b 59 311 31(M h 1949)

marrow attributable to carcity of leukocyte precursors and replacement by plasma cell From bacteriologic studies it was concluded that a human strain of Mycobacterium tuberculosis was responsible

pulmonary tuberculosis in adults except that gross caseation of tracheobronchial lymph nodes infrequent in adults was present in 7 of the 20 children

Twenty one children had active tuberculosis of bone and 10 9 of whom were girls had urogenital tuberculosis In 37 tuberculous meningitis was the cause of death and there were tuberculomas in 27 brains One patient had tuberculous valvular endocarditis of mitral and aortic valves

Fulminant Tuberculous Septicemia with Leukopenia Walter Pagel and A L Woolf[6] (London) present the twelfth case in the literature of rapid generalized tuberculosis which either fails to cause detectable lesions or produces multiple necrotic areas which do not resemble classic tubercles but contain tubercle bacilli Since in most cases the patients have shown primary abdominal infection diagnosis is usually made from a fulminant clinical picture often resembling typhoid fever in conjunction with anatomic changes rather than by a positive blood culture for the organisms

Man 56 was well until one month before hospitalization when he fainted in the street Improvement was slow and anorexia disinterest increasing deafness and rash on face arms and legs persisted five days before admission the face twitched The temperature was 101 F total leukocyte count 2 050/cu mm and a chest x ray showed patchy consolidation and partial collapse of the right lower lobe Leukocyte count fell to 250/cu mm lungs became increasingly congested cerebrospinal fluid cell count increased from 1 to 156/cu mm and the patient died eight days after hospitalization

At autopsy microscopic areas of necrosis were noted in most organs but few gross changes were visible In the right lower lobe was a subpleural wedge shaped area of confluent caseous bronchopneumonia containing many acid fast bacilli but no classic tubercles This lesion in conjunction with massive necrosis of bifurcation lymph nodes constituted a primary complex of short duration Postmortem lung x rays showed no trace of a preceding calcified primary infection There was fibrinoid necrosis of the intima of larger veins in the spleen in association with numerou acid fast bacilli (Fig

(6) Am Rev Tub rc 59 311 316 Ma h 1949

considers a manifestation of tuberculous allergy it occurs in a small percentage of patients with tuberculosis Fever is a more common sign lasting several days or weeks and may be slight or high continual or remittent A tuberculin reaction in a febrile child previously tuberculin negative is of diagnostic significance Sedimentation rate rises even in patients in whom careful check on temperature at end of incubation period discloses no fever

Normally incubation may vary from three to eight weeks but streptomycin treatment during incubation may prolong the period In one of Wallgren s patients streptomycin prolonged incubation period to four months

The second stage follows immediately lasts about three months and coincides with the malignant generalized forms miliary tuberculosis and meningitis These result from hematogenous spread of tubercle bacilli from the primary complex It is rarely possible to demonstrate this spread by blood culture but tubercle bacilli may be found in urine during this period An infected person who has survived this period successfully is not likely to contract tuberculous meningitis or miliary tuberculosis

The third stage during which pleurisy may develop starts about three months after manifestation of the primary infection and lasts approximately four months Rarely does an infected person who has had pleurisy contract meningitis It is not known why the predilection to pleurisy occurs at this period Pleurisy is generally considered an allergic manifestation of tuberculosis and is thought to depend on both specific tuberculous infection of pleura and specific hypersensitivity of pleura

The fourth stage lasts until the primary complex has healed i e approximately three years after infection This is the period of skeletal tuberculosis In persons with primary infection in adolescence this stage also corresponds to the period of postprimary pulmonary tuberculosis

Local Recrudescence as Endogenous Source of Phthisis A L Woolf[7] (London) reports four cases in which evidence of local recrudescence of tuberculosis during severe concomitant disease was demonstrated at autopsy Calcified spots coexisted with liquefied areas in old tuberculous lesions and there were collections of great numbers of tubercle bacilli in circumscribed foci in which liquefaction was beginning Presence of fresh liquefaction closely associated with old caseous and calcified areas makes it apparent that such lesions were not incompletely calcified healing lesions Factors undoubtedly favoring reactivation of old tuberculous lesions in three patients were carcinomatous cachexia with starvation diabetes and exposure to hardship as prisoners of war followed by subacute bacterial endocarditis

It is particularly important that in these cases bacillary multiplication was demonstrated as the leading event in liquefaction Some areas were seen in which tissue had disintegrated at the site where large numbers of acid fast rods had collected in the absence of leukocytic or mononuclear cell infiltration These changes are interpreted as representing very early stages of liquefaction before tissue destruction by action of polymorphonuclear leukocytes and other inflammatory cells

Evidence of endogenous development of tuberculosis in these patients and for further bronchogenic spread seems well established Actual origin of the focus whether exogenous or hematogenous primary or post primary appears less important than the fact of long standing presence and final breakdown

Timetable of Tuberculosis has been worked out by Arvid Wallgren[8] (Karolinska Inst Stockholm) Tuberculosis passes through several characteristic periods The first stage is reached five or six weeks after infection and is characterized by tuberculin sensitivity fever erythema *nodosum* and the primary complex Erythema nodosum is a nonspecific allergic phenomenon which Wallgren

(7) Tube 1 29 § 230 Octobe 1948
(8) Ibid pp 46 51 Novemb 1948

[The most dependable procedure should be u ed for recovery of tubercle bacilli On thi account gastric lavage is preferred how ever the laryngeal swab may have a place when the element of time i important and personnel is limited —Ed]

Bronchial Lavage in Detection of Tubercle Bacilli Brian C Thompson A O M Gilmour and L G Ellis[1] (Otago Hosp Board) performed bronchial lavage on 20 patients all normally sputum free and gained a yield of secretion from each individual in some as much as 50 cc The patients found the procedure less disagreeable than gastric lavage Findings were positive in 24 hours for six patients while culture of bronchial material was positive in one and of gastric material in five only after several weeks

METHOD —Bueno s technic was used The patient sat up in bed holding his tongue forward The oral pharynx and epi glottis were generously sprayed with 2 per cent solution of butyn® When swallowing was paralyzed the operator grasped the patient s tongue with the left hand and passed the curved nozzle of a laryngeal syringe over back of the tongue into the larynx with the right hand During a deep inspiration 20 cc warm sterile normal saline solution was injected and if too much was coughed up at once 10 cc more was injected While lying flat and turning from one side to the other the patient coughed intermittently during the next half hour and all expectoration was deposited through a sterile funnel into a sterile glass bottle

The bottle s contents were treated with an equal portion of saturated solution of trisodium phosphate and incubated 24 hours at 37 C After neutralization with 25 per cent hydro chloric acid and centrifugation at 300 rpm for 15 minutes the deposit was examined by direct smear or by culture

[There is a strong theoretical objection to this procedure since it is known that thin liquids in the lungs may when contaminated with tubercle bacilli tran mit these to healthy parts of the lung giving rise to new lesions Such lesions may be small and may not become evident for some time afterward This seems to be a legiti mate reason for not adopting the procedure —Ed]

Rapid Mouse Test for Laboratory Diagnosis of Tu berculosis Albert Milzer and Edwin R Levine (Mi chael Reese Hosp Chicago) used gastric mucin for en hancing the virulence of H37Rv and several recently iso lated strains of mammalian tubercle bacilli for pigmented

(1) N w Z l d M J 48 7 10 F bru ry 1949
(2) P S E p B l & M d 69 16 17 O t be 1948

Study of the timetable of tuberculosis acquaints the clinician with the dangers in the periods after contraction of the disease

[Some of these phases following primary infection are very inconspicuous when the infection is postponed until late adolescence Hematogenous dissemination at that time occurs to a lesser degree and apparently less frequently than it does in infancy and early childhood.—Ed]

Laryngeal Swab in Early and Convalescent Cases of Pulmonary Tuberculosis G B Forbes B J D Smith J V Hurford and V H Springett[9] compare results of cultural examination of fasting gastric contents for tubercle bacilli with those of laryngeal swabs They studied 100 inpatients and 101 outpatients with x ray evidence of pulmonary tuberculosis but with microscopically negative or no sputum In inpatients gastric lavage gave 10 per cent more positive results than the swabs Of this group 55 patients had received collapse therapy and 19 could be regarded clinically as effectively treated However 4 of the 19 gave positive gastric lavage cultures and 2 positive laryngeal swab cultures Tubercle bacilli were cultured by one or both methods from *22 of 34* patients in whom collapse treatment was regarded as having been only partially effective

The outpatients all had tuberculosis detected by mass x ray surveys and were free from symptoms severe enough to cause them to consult a physician There was no difference in the proportions of positive results obtained by the two methods in this group Cultures were negative by both methods in *82* patients and positive by *one or both methods in 19*

In both groups 45 patients were positive by laryngeal swab and 53 by gastric lavage Patients preferred the laryngeal swab method The laboratory technic for laryngeal swab is simpler and less time consuming than that for gastric lavage However it is not suggested that either method replace cultural examination of expectorated sputum since it yields results much superior to those of the laryngeal swab method

(9) La t 2 141 143 J ly 24 1948

low pleural fluid sugar value It may be recalled that a low cerebrospinal fluid sugar value is often helpful in the diagnosis of tuberculous meningitis Some years ago Pinner and Moerke (Am Rev Tuberc. 2 121 183 1930) reported elaborate studies of chemistry and other features of pleural effusions They noted the low sugar content of tuberculous effusions but doubted its diagnostic value — Ed]

Bronchoscopic Studies in Primary Tuberculosis in Childhood Eliasberg and Neuland in 1920 described epituberculosis as a disease in children passing through primary tuberculous infection with extensive x ray shadows in the lungs but without the usual symptoms of tuberculous pneumonia As the children recover the shadows disappear without leaving evidence of permanent lung disease James H Hutchison[4] (Univ of Glasgow) examined 30 children with epituberculosis bronchoscopically and presents evidence that it is due to absorption collapse caused by bronchial obstruction Eighteen had active pulmonary tuberculosis associated with sharply outlined x ray shadows in lung fields but without mediastinal or tracheal displacement 10 had active primary tuberculosis with similar signs plus mediastinal or tracheal shift and two had uninfected bronchiectasis complicating a healed primary tuberculous infection In two of those with mediastinal or tracheal shift obstructive emphysema (Fig 31) was also seen

In 2 patients with active primary tuberculosis no bronchial abnormality was found but the other 26 presented several types In type I (nine patients) the bronchial lumen was narrowed by local bulging of the wall and the mucosa over the bulge was hyperemic and swollen This appearance was due to extrinsic pressure on the bronchial wall by tuberculous bronchopulmonary lymph nodes

In type II *a* (three patients) under the mucosa covering the bulge were glistening yellow slightly raised areas indicating that a caseous lymph node was on the verge of pointing into the lumen On one occasion accidental rupture produced semifluid caseous material rich in

(4) Q t J M d 18 1 49 J y 1949

(C3H or dba) mice By this method tubercle bacilli were isolated from 14 patients 10 15 days after inoculation Some positive results in mice were obtained with microscopically negative sputum

METHOD—Patient s sputum or feces was prepared in the usual manner mixed with equal parts of 5 per cent mucin (5 Gm granular mucin type 1701 W Wilson Laboratorie in 100 cc distilled water adjusted to pH 7 4 and autoclaved) and 0 5 cc inoculated both subcutaneously and intraperito neally into each of four or five C3H or dba mice Saline sus pensions of lesions were planted in Petragnani s medium and impression smears of spleen liver and peritoneal fluid were routinely made because acid fast bacilli can sometimes be dem onstrated although no macroscopic lesions are present Feeding the Dubos and Pierce cornmeal gelatin butter diet to pig mented mice inoculated with mucin increased the number of isolations from patients

[The need is generally recognized for a means of recovering tubercle bacilli in the shortest possible time hence the value of this study For the same reason the slide culture method of Pryce (J Path & Bact 53 327 1941) has continued to attract interest. Cummings and Drummond (Am Rev Tuberc 59 599 May 1949) have adapted this method for the earlier determination of streptomycin sensitivity They are able to make the determination in a week compared with the usual time of about six weeks—Ed]

Relation of Pleural Fluid Sugar to Pulmonary Tuberculosis Stephen M Gelenger and Russell F Wiggers[3] (Flint Mich) determined pleural fluid sugar concentrations in 33 cases of pleural effusion All of eight patients with pleural fluid sugar value below 30 mg per cent had tuberculosis Among four with sugar values between 30 and 60 mg per cent two had tuberculosis Pleural effusion was not due to tuberculosis in any of the 21 patients with pleural fluid sugar levels above 61 mg per cent

No patient with tuberculosis had a level above 39 5 mg and average sugar value for tuberculous patients was 15 7 mg per cent Levels of 30 mg per cent or less should be considered diagnostic of tuberculosis and borderline values should be considered a sign of tuberculosis until proved otherwise

[These estimations are made in a rather small group and should be amplified in view of the presumed diagnostic significance of a

(3) D of Ch t 15 3 5 3 ? M h 1949

of typical tuberculous tissue and was presumably a more advanced stage of type II b

In one patient with healed primary tuberculosis there was a greatly narrowed and puckered middle lobe bronchus and a lipiodol[*] bronchogram showed complete occlusion of this bronchus 1 cm from its origin In the second patient with healed lesions the right bronchial tree was distorted and a bronchogram showed cylindric bronchiectasis in the right lower lobe These cases illustrate that epituberculosis may leave permanent severe damage although it is not known how frequently

In 15 cases the carina major was appreciably widened indicating involvement of inferior tracheobronchial lymph nodes by the tuberculous process

Findings in this series suggest that absorption collapse occurs in most cases of epituberculosis It is caused by bronchial obstruction due to pressure on the wall by enlarged tuberculous lymph nodes Incomplete occlusion may cause obstructive emphysema this was observed in two patients Absorption collapse may not be associated with much diminution in lung volume if bronchial occlusion is produced slowly and especially if there is lung parenchyma disease in addition Bronchoscopy permits exclusion of pulmonary collapse due to inhalation of a foreign body

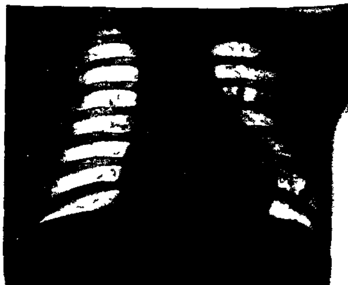
[So-called epituberculosis is often found actually to represent *tuberculous pneumonia* or *nonspecific pneumonia* caused by bronchial obstruction It is not often that a lymph node ulcerates through the wall of the bronchus or trachea although this is observed more frequently in infants and young children than in older patients — Ed.]

Minimal Pulmonary Tuberculosis Its Significance in Relation to Age of Patient. From a study of 164 minimal infections Robert Chang[5] (Rutland Mass State Sanatorium) concludes that early infiltrates are chiefly found in patients under 25 and fibroid minimal lesions in patients over 25 Mixed type lesions were present in 47 patients under 25 in 39 aged 25 38 and in 17 over 38 Of 119 clinically active cases 9 3 per cent were negative

(5) *Am R T berc* 58 612 618 Decemb 1948

tubercle bacilli Presumably this happens frequently in natural circumstances In type II *b* (two patients) the bulge was more circumscribed and pinkish yellow forming a tuberculoma the covering mucosa was intact Histologically such a tuberculoma consists of tuberculous tissue

In type III *a* (seven patients) there was an area of ulceration in the bronchial mucosa covered by a thin



Fg 31—Ob t t v mphy m f ght l g w th m d t l b ft to l ft nd g tal ll p f ght l w r l b

layer of granulation tissue either dirty yellow or raspberry red which bled readily It was not possible to determine whether this was the sequel to rupture or whether a lymph node was slowly eroding through the bronchial wall In type III *b* (five patients) a main bronchus or primary division to a lobe was filled with pinkish or grayish yellow friable granulation tissue which could often be dislodged readily with the sucker without much bleeding Histologically it omposed

of typical tuberculous tissue and was presumably a more advanced stage of type II *b*

In one patient with healed primary tuberculosis there was a greatly narrowed and puckered middle lobe bronchus and a lipiodol® bronchogram showed complete occlusion of this bronchus 1 cm from its origin In the second patient with healed lesions the right bronchial tree was distorted and a bronchogram showed cylindric bronchiectasis in the right lower lobe These cases illustrate that epituberculosis may leave permanent severe damage although it is not known how frequently

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for tubercle bacilli by all available method X rays of patients with negative sputum indicated exudative and rapidly resolving disease Sedimentation rate and white cell counts were of little use in determining activity

More than half the patients with incipient disease denied symptoms at any time Commonest complaints were fatigue (42 6 per cent) and cough (35 4 per cent) Hemoptysis before admission was reported by 18 3 per cent one third of whom had inactive lesions In older patients symptoms are of lesser importance in deciding activity and their absence strongly suggests inactivity Any symptom of younger patients should be carefully evaluated and absence of symptoms never considered evidence of inactivity

In patients under 25 88 9 per cent of lesions were active whereas in those over 38 only 48 8 per cent were active Regardless of their character lesions in younger patients had a much higher rate of progression than those in the older group

Patients under 25 stayed at a sanatorium an average of 482 days whereas older patients stayed 283 days Pneumothorax was given 60 7 per cent of patients under 25 44 2 per cent of those aged 26-38 and none over 38 There were two deaths from progressive tuberculosis but the other 162 patients were discharged with apparently arrested or quiescent disease Among those with active lesions 17 had reactivations whereas none occurred among the 45 considered to have inactive lesions

Prolonged study with serial x rays and intensive bacteriologic examinations may be necessary to determine the potentialities of a minimal lesion Younger patients should spend the observation period in a sanatorium

[This study again emphasizes the importance of age in estimating the potentialities of tuberculosis Chang has resorted to artificial pneumothorax for minimal pulmonary disease more often than many clinicians Under early treatment with bed rest the recovery rate without pneumothorax is usually reported as 80 90 per cent

Many of the recent studies on the use of streptomycin in tuberculosis have been concerned with optimal dosage particularly in relation to toxicity effectiveness and development of drug re

sistance The following articles summarize exten ive experiences and thr w considerable light on these question Generally speak ing experience indicates that development of str ptomyc n re si tance depends more on the duration of treatment than on the daily dose resistance usually begins to emerge after a month of therapy and increases rapidly after six w eks U ually when re sistance is demonstrated no further therapeutic effect i to be expected There are a few exceptions some of which may be ex plained by the observation that organ m in different lesion may be differently affected and some may remain sensitive If reactiva tion or extension from such a lesion occurs the drug may be effective Lenert and Hobby (Am Rev Tuberc 59 219 220 February 1949) noted streptomycin dependent strains of Mycobac terium tuberculosis in otherwise sensitive culture These appear to be rare but a these observers suggest streptomycin might pro mote the growth of such strains and thus lim t the therap utic effects

Because of the toxicity of large doses of streptomycin mo t clinicians now advise a dose of 1 Gm daily Small r doses are probably less effective As a rule the drug is given daily although in som ca es effects may be observed when it i given at intervals of two or more days but the limitations and place of such sched ules have not been clearly defined

Streptomycin like other chemotherapeutic agents ha its most striking effect in cases of acute or subacute tuberculosi without extensive necrosis e g early tuberculou pneumonia In some the in tial favorable response is followed by an early relapse and in none is it to be expected that chemotherapy is the final an wer All patients mu t have prolonged rest treatm nt to permit healing of necrotic and ulcerative lesions which requires many months be cau e of the slowness of fibro is —Ed]

Streptomycin in Treatment of Tuberculosis Current Status[6] The second annual progress report on a co operative investigation by the Veterans Administration Army and Navy since June 1946 includes observations on 2 800 patients with all types of tuberculosis who have completed treatment with streptomycin in 48 hospitals Reduction in daily streptomycin dosage from 2 0 Gm to 1 0 Gm and further reduction to 0 5 Gm was accom panied by significant reduction of toxic manifestations (see Table) With dosage reduction and division into two rather than five injections daily therapeutic efficacy does not seem impaired More prolonged observation of tuberculosis of bone joints and genitourinary tract has led to a more optimistic view of treatment

In 943 cases of pulmonary tuberculosis streptomycin

(6) J A M A 138 584 593 Oct 3 1948

1 0 Gm daily for 60 days was as effective as 2 0 Gm daily for 120 days Streptomycin in conjunction with bed rest reverses the trend of progressive predominantly exudative moderately and far advanced disease in an astonishing number of cases Because of a large percentage of relapses and complete clearing is unusual streptomycin therapy is rarely definitive Its greatest useful

TOXIC MANIFESTATIONS OF STREPTOMYCIN IN 1751 PATIENTS WITH TUBERCULOSIS

	Regimen				
	1 8 2 0 G (5 d) 1 0 d	0 Gm (5 d) 60 da	1 0 Gm (5 1 d) 120 da	1 0 Gm (d) 120 d	0 5 Gm (d) 1 0 d
Patients treated*	671	177	321	445	137
Toxicity incidence (%)					
Compelled cessation treatment	9 9	6 4	5 0	2 0	0 0
Vertigo	80 0	62 7	34 3	23 1	5 8
Ataxia	45 0	26 0	20 6	11 5	2 9
Caloric stimulation no response	34 1	41 2	10 3	5 4	0 0
Caloric stimulation diminished response	27 1	34 7	23 9	25 2	27 8
Hearing diminished voice	2 7	0 6	0 3	0 2	0 0
Hearing diminished audiometer	13 8	19.2	4 0	9 5	11 7
Renal function diminished	9.2	10 8	7 8	5 8	2.2
Albuminuria	24 4	19 8	17 1	11 0	15.3
Dermatitis severe	4 6	1 1	1 2	1 1	0 7
Dermatitis mild	10 0	5 6	5 6	4 7	2 2
Eosinophilia >6%	63 5	49 2	36 8	34 6	31 5
Fever	5 7	2 8	0 0	1 8	0 0
Blood dyscrasia	0 6	2.3	0 9	0 7	0 7

An e r r w d l b tely t odu d to l mn 5 (0 5 Gm) b dd g p t ents who h d ot y t mpl ted th fi al 60 days of t atm nt

ness appears to lie in conjunction with collapse therapy Optimal time to induce collapse is during the first weeks of streptomycin therapy before micro organisms become resistant It should not be used for minimal tuberculosis or any other lesion which may be expected to respond favorably lest one be faced with a life threatening episode in the future and be unable to use streptomycin because of resistance developed by the organism during previous therapy Streptomycin did not affect favorably the x ray picture in long established fibrous or caseous

lesions Its effect on cavities was unpredictable and often when favorable fleeting

Study of 112 cases of tracheobronchial and 166 cases of laryngeal tuberculosis led to the conclusion that improvement could be expected in 80 90 per cent of such cases making this one of the most favorable fields for streptomycin therapy Administration of streptomycin by aerosol was ineffective Streptomycin cannot be expected to affect the underlying pulmonary pathologic condition in these cases and relapses may be anticipated However the prompt enormous improvement in symptoms of laryngitis was significant

Streptomycin treatment of 368 patients with 674 cutaneous sinuses and fistulas caused approximately 4 of 5 such lesions to heal in an average of eight weeks Sinuses originating in bone healed more frequently than those with other origins and fistulas connecting with pleura did least well In one third of the patients pus was evacuated and necrotic tissue of bone removed either at start of streptomycin therapy or shortly thereafter A regimen of 1 0 Gm daily was as effective as larger doses and smaller doses may be equally useful

A review of 260 patients showed that immediate clinical response and resolution of pulmonary lesions made continued use of streptomycin mandatory for tuberculous meningitis and acute miliary tuberculosis End results in terms of surviving patients are remarkable in comparison with prestreptomycin days but less so than had been hoped Little or nothing has been learned about the most effective regimen—duration dosage or route of administration

Review of 27 patients suggested that streptomycin was of value in acute and chronic exudative adhesive or caseous tuberculous peritonitis

Although prophylactic use of streptomycin significantly decreased incidence of post thoracoplasty spread routine use was not justified because incidence of spread was low in patients who did not receive streptomycin Its use here constitutes wa te of the drug and introduce

1.0 Gm daily for 60 days was as effective as 20 Gm daily for 120 days. Streptomycin in conjunction with bed rest reverses the trend of progressive predominantly exudative moderately and far advanced disease in an astonishing number of cases. Because of a large percentage of relapses and complete clearing is unusual, streptomycin therapy is rarely definitive. Its greatest usefulness

TOXIC MANIFESTATIONS OF STREPTOMYCIN IN 1,751 PATIENTS WITH TUBERCULOSIS

	REGIME				
	1.8-2.0 Gm. (5 d.) 120 da.	2.0 Gm. (5 d.) 60 da.	1.0 Gm. (5 d.) 120 da.	1.0 Gm. (5 d.) 120 da.	3 Gm. (d.) 120 da.
Patients treated	671	177	321	445	135
Toxicity incidence (%)					
Compelled cessation treatment	9.9	6.4	5.0	2.0	0.0
Vertigo	80.0	62.7	34.3	23.1	[illegible]
Ataxia	45.0	26.0	20.6	11.5	[illegible]
Caloric stimulation, no response	34.1	41.2	10.3	5.4	0.0
Caloric stimulation diminished response	27.1	34.7	23.9	25.2	2.8
Hearing diminished voice	2.7	0.6	0.3	0.2	0.0
Hearing diminished audiometer	13.8	19.2	4.0	9.5	11.7
Renal function diminished	9.2	10.8	7.8	5.8	2.2
Albuminuria	24.4	19.8	17.1	11.0	15.3
Dermatitis severe	4.6	1.1	1.2	1.1	0.7
Dermatitis mild	10.0	5.6	5.6	4.7	2.2
Eosinophilia, >6%	63.5	49.2	36.8	34.6	31.5
Fever	5.7	2.8	0.0	1.8	0.0
Blood dyscrasia	0.6	2.3	0.9	0.7	0.7

An er o wa del be t ly i trod ced nto col m 5 (0.5 Gm.) b al g patients who had not yet completed their final 60 days of treatment.

ness appears to lie in conjunction with collapse therapy. Optimal time to induce collapse is during the first weeks of streptomycin therapy before micro-organisms become resistant. It should not be used for minimal tuberculosis or any other lesion which may be expected to respond favorably lest one be faced with a life threatening episode in the future and be unable to use streptomycin because of resistance developed by the organism during previous therapy. Streptomycin did not affect favorably the x-ray picture in long-established fibrous or caseous

per se An accumulating mass of evidence suggests that a resistant culture means further treatment with streptomycin is useless and conceivably dangerous Assuming that a resistant culture means a resistant patient the public health hazard involved is rather obvious All new cases of tuberculosis contracted from streptomycin resistant patients are unsuitable for treatment with streptomycin The question of how to avoid this situation remains to be answered

Streptomycin Treatment of Pulmonary Tuberculosis Medical Research Council Investigation.[7] All of 55 patients who were to receive streptomycin and 52 control patients had acute progressive bilateral pulmonary tuberculosis of presumably recent origin bacteriologically proved and unsuitable for collapse therapy and were between ages 15 and 30 During the preliminary observation week maximal evening temperature was 101 F or more in 24 streptomycin patients and 19 controls Large or multiple cavities were seen on the admission x ray of 32 streptomycin patients and 30 controls Those who received streptomycin were given four daily 0 5 Gm intramuscular injections at six hour intervals for four months

After six months eight streptomycin treated patients with temperature of 101 F or over showed considerable improvement but none of the controls had improved At two months 76 per cent of streptomycin treated patients showed x ray improvement and in 14 per cent the improvement was considerable 11 per cent were worse and none had died Only 6 per cent of control patients had improved none considerably 38 per cent were worse and 4 per cent had died During the third and fourth months 65 per cent of streptomycin treated patients improved 14 per cent had deteriorated and none had died Among controls 18 per cent had improved 42 per cent were worse and 19 per cent had died In the fifth and sixth months 34 per cent of streptomycin treated patients improved 31 per cent deteriorated and 7 per cent died Among controls surviving at four months

the hazard of producing resistance Spreads which de veloped postoperatively usually responded satisfactorily to streptomycin It was agreed that streptomycin should be used routinely after pneumonectomies and lobec tomies in only 4 of 144 patients treated prophylactically with streptomycin did postoperative spread develop

Besides toxic reactions prolonged streptomycin ther apy may be complicated by the resistance tubercle bacilli

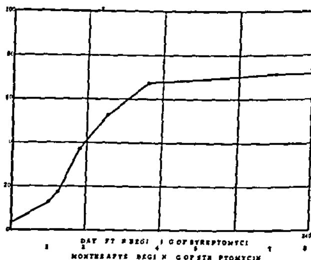


Fig 3 —D 1 m t of e t ce by My b te m t be cul t st p tomy C lumn f fig s t I ft h w pe c tage of cult r tant to m th 10 m og m /cc m d m (C t y f Co ncl of Ih ma y d Chem t y J A M A 138 584 593 Oct 23 1948)

develop to it Figure 32 shows the time relationship with which this resistance developed in 2 100 cultures Most resistant cultures grew in more than 100 $\mu g/cc$ and many grew in more than 1 000 $\mu g/cc$ Successive cul tures from the same patient usually grow in progres sively higher concentrations of streptomycin as treat ment continues The occasional instance in which re sistance having been developed subsequent cultures again become sensitive may arise from technical error in determination rather than from true loss of resistance

tion was obtained from eight investigators on 332 patients with pulmonary tuberculosis who had completed streptomycin therapy and had been observed at least 90 days after beginning treatment Disease was minimal in 17 moderately advanced in 118 and far advanced in 197 80 per cent had predominantly acute or subacute and the remainder chronic disease Tuberculosis involved trachea bronchi and larynx in 125 lymph nodes with sinus tracts in 18 intestinal tract in 16 bones and joints in 13 genitourinary tract in 10 and miscellaneous sites in 22 Most patients were white 200 were female and 66 per cent were between 20 and 39

The effectiveness of streptomycin is fundamentally related *to type and extent of pathology It was most effective* against acute exudative and least effective against extensive predominantly chronic disease Subacute disease was improved less than acute but more than chronic disease Since progression of chronic tuberculosis is fundamentally related to occurrence of acute *episodes use of short courses of streptomycin to combat* such episodes should be stressed

Clinical improvement occurred in 86 per cent of patients receiving 1 5 3 Gm /day in contrast to 65 per cent of patients who received 0 5 1 4 Gm /day Among those treated 90 days or more 78 per cent showed clinical improvement whereas 66 per cent treated 30 89 days improved X ray improvement was noted in 82 per cent receiving the larger daily doses and in 54 per cent receiving the smaller amounts Over all x ray improvement seemed to be related to duration of treatment but to a much lesser extent than to dosage In general relation between closure of cavities total daily dosage and duration of treatment was similar to that for over all x ray and clinical improvement

Sputum conversion occurred in 63 per cent of those receiving the larger and 38 per cent of those receiving the smaller doses Conversion occurred in 58 per cent of patients treated over 90 days and in 36 per cent of those treated 30 89 days The high percentages of sputum con

10 per cent died and 26 per cent deteriorated 10 patients improved Nearly all streptomycin treated patients who had deteriorated in the first months continued to get worse subsequently Control patients who improved did so much more slowly than streptomycin treated patients

Of 28 streptomycin treated patients whose x rays had improved considerably at the end of six months 11 had been regarded as desperately ill on admission Clinical improvement in all respects was noted in 21 and in 8 sputum had become negative to all examinations for tubercle bacilli Considerable improvement in the x ray picture was reported for only four controls none of whom had been acutely ill on admission and in none of whom had sputum become negative

Toxic effects of streptomycin were observed in many patients but in none did they necessitate suspension of treatment Strains with resistance over 10 times that of H37Rv were found in 35 of 41 cases The mean date of resistance emergence was 53 days after initiation of therapy Streptomycin resistance was probably responsible for most of the deterioration seen in streptomycin treated patients after initial improvement

Six months after admission general condition of 33 streptomycin treated patients (60 per cent) and of 24 control patients (46 per cent) was better than on admission 13 streptomycin treated patients (24 per cent) were worse and 4 others (7 per cent) had died 12 controls (23 per cent) were worse and 14 (27 per cent) had died One year after admission 31 streptomycin treated patients (56 per cent) and 16 controls (31 per cent) showed improvement, 8 streptomycin treated patients (15 per cent) and 7 controls (13 per cent) were worse 12 streptomycin treated patients (22 per cent) and 24 controls (46 per cent) had died and in the remainder there was no change

Streptomycin Tuberculosis Research Project of American Trudeau Society Summary Report is presented by H McLeod Riggins and H Corwin Hinshaw [8] Informa

(8) Am R Tuber 59 140 167 F b a y 1949

was not subsequently established were not included in the present series The report was compiled from information contained in progress reports submitted every two weeks to a central committee by 47 Veterans Administration hospitals and five civilian hospitals under contract with the Administration The 100 patients included in the survey were males aged 17-64 Pre existing tuberculous foci of lungs genitourinary tract lymph nodes or bone and joint were found in 92 Twenty two had miliary tuberculosis without meningitis 10 miliary tuberculosis followed during or after cessation of therapy by meningitis 25 both miliary and meningitic tuberculosis when treatment was instituted and 43 meningitis without miliary tuberculosis

Of the 22 with miliary tuberculosis but no meningitis 3 died during therapy without showing any response to treatment 3 responded temporarily but then died and 16 survived One is in terminal stages of tuberculosis and another has not shown significant improvement X rays of nine persons showed complete resolution and those of the other five showed marked reduction in size and number of lesions Associated foci originally present in 15 of the 16 survivors regressed in 7 and in 5 others became arrested Lesions of the other three have continued to be active

Of six patients in whom meningitis developed during streptomycin therapy for miliary tuberculosis five died and one is in terminal stages of tuberculosis In four patients tuberculous meningitis developed after cessation of treatment for miliary lesions Of these two died A third is not likely to survive and the fourth is apparently in complete remission from both miliary and meningeal tuberculosis In contrast to the ineffectiveness of streptomycin in meningeal lesions miliary lesions resolved markedly in 8 of 10 patients during therapy

Of 25 patients with miliary and meningitic tuberculosis at onset of treatment 20 died and pronounced clinical improvement occurred in the other 5 but was not maintained Only one case can be considered a therapeutic

version would probably be much lower if they were based on repeated examination by culture or animal inoculation Not infrequently sputum again became positive for tubercle bacilli

Of 159 patients 56 (35 2 per cent) discharged tubercle bacilli resistant to 10 or more μg streptomycin/ml after various periods usually two or more months from beginning of treatment Had sensitivity tests been possible in all patients at the end of prolonged treatment incidence of significantly resistant strains probably would have been much greater Emergence of organisms resistant to more than 10 μg/ml was more rapid in patients receiving the larger daily doses than in those receiving the smaller However the percentage of those receiving the smaller daily doses in whom resistant strains emerged was larger

The frequency and severity of toxicity was greater in patients receiving the larger daily dosages In order of importance and frequency toxic manifestations encountered were vestibular dysfunction eosinophilia nausea and vomiting transient renal irritation or damage dermatitis and drug pyrexia The great majority of reactions were reversible labyrinthine dysfunction either being reversible or compensated for in almost all cases

Although percentage of relapse was essentially the same in the different groups the larger doses for the longer periods seemed to be more effective It is emphasized that optimal daily dosage must be individualized as in other drug therapy In chronic disease more definitive treatment notably collapse therapy must be used if lasting results are to be achieved

One Hundred Cases of Miliary and Meningeal Tuberculosis Treated with Streptomycin are reviewed by Paul A Bunn[9] (Washington D C) In April 1946 streptomycin became available for treatment of miliary and meningeal tuberculosis in Veterans Administration hospitals Presumptive diagnosis was accepted as a basis for initiating therapy but patients in whom diagnosis

(9) Am J M S 216 6 315 Sept mo r 1948

healed within nine and four weeks after therapy was started and both were still healed nine months later In another patient old and recurrently active tuberculous laryngitis of 10 years standing progressed steadily for six months before streptomycin therapy to which re sponse was dramatic After four months of treatment the larynx was essentially normal and during the subse quent year remained healed

In six patients with single or multiple thin walled cavi ties not associated with dense fibrosis the cavities had increased in size or remained unchanged during six or more months of observation at bed rest During treat ment with streptomycin all cavities in four patients ap peared to close and cavities in the other two were greatly reduced In two patients cavities reopened The authors conclude that streptomycin alone will only occasionally accomplish permanent closure of cavities but may be an extremely valuable supplement to bed rest and collapse therapy A representative case follows

Woman 21 was hospitalized because of pulmonary symp toms of six months duration X rays showed disseminated small nodular infiltration throughout both lungs with three thin walled cavities The patient failed to improve at bed rest Treatment with streptomycin 1 8 Gm daily was then instituted and continued for 120 days On completion of treatment there was striking clinical improvement sputum was consistently negative for tubercle bacilli and roentgenograms (Fig 34) showed considerable clearing of the disseminated nodular *disease present at onset of treatment (Fig 33) During treat* ment there was complete closure of all cavities In the following 10 months further clearing was evident in x rays and sputum and gastric contents remained consistently negative

The third group of patients in whom streptomycin was used had chronic low grade pulmonary infection which was never arrested completely despite long often multi ple periods of sanatorium treatment and trials of phrenic paralysis and pneumothorax where indicated Sputa re mained positive for tubercle bacilli on most examina tions and recurrent exacerbations of the disease as determined by x rays were the rule In most patients the disease was bilateral In none could persistence be ex

success though lives of 10 patients were prolonged and in 8 pulmonary dissemination cleared entirely

The most spectacular and decisive effect was noted in patients with tuberculous meningitis without miliary tuberculosis Of 43 such patients 16 are alive 4-14 months after institution of therapy and in 11 others life span was prolonged Of the 16 patients still alive 10 are free from all signs of infection In the other six results of therapy cannot be thoroughly evaluated

Toxic reactions occurred in 28 patients In 20 there was hearing loss in 13 kidney damage in 4 exfoliative dermatitis and in 2 granulocytopenia

[This report indicates that early results of streptomycin treatment in miliary and meningeal tuberculosis are dramatic though relapse is very frequent The experience of Edith M Lincoln with meningitis in children at Bellevue Hospital has been more favorable She has used the following average course of treatment streptomycin 100-50 mg for 40 injections (average period 60 days) streptomycin intramuscularly 1 Gm. daily for 180 days promizole * sufficient to give blood level of 1 3 mg per cent, continued for many months sometimes two years Five of the 21 children so treated have died follow up varying from a few to 27 month Organisms in the cerebrospinal fluid do not become resistant to streptomycin as early as they do in the sputum according to some studies

Scheidegger and Staehelen Schlienger (Schweiz Ztschr f Tuberk. 5 352 364 1948) describe autopsy observations in two cases after treatment with 193 and 172 Gm streptomycin. The healing tendency of the lesions was much less marked in the meninges than in the lungs and other organs The process in the meninges gave evidence of a chronic progressive course with endangiitis The brain and spinal cord showed malacia and there were nonspecific inflammatory changes in the peripheral nerves myocardial damage possibly due to the drug was noted Such experiences indicate the desirability of improving treatment for generalized tuberculosis —Ed]

Treatment of Tuberculosis with Streptomycin Response of Certain Subacute and Chronic Types Acute tracheobronchial tuberculosis responds well to streptomycin but less is known of its effect in chronic cases Kirby S Howlett Jr and John B O Connor[1] (Shelton Conn) report excellent response of two patients with chronic ulcerative tuberculous bronchitis One lesion had been present over 5 years and the other over 2½ years before streptomycin treatment was instituted The lesions

(1) Am. Rev T berc 58 139 17 A gu t 1948

plained entirely by presence of endobronchial disease or cavities *In no case had this status existed less than a* year and in most it had existed for over two years Eleven patients were treated with streptomycin and observed for six months or longer Two patients received 2 Gm daily for 120 days one 2 Gm daily for 62 days and eight 1 Gm daily for 42 days X ray improvement was never more than slight except in one case in which the cavity closed Nevertheless eight patients had an improved sense of well being weight gain and reduced expectoration Definite hardening and retraction of some of the densities were seen on x rays in eight cases Definitive evaluation of streptomycin in these patients cannot be made at this time Complete and sustained sputum conversion was achieved in only a few patients Results in this type of tuberculosis do not in the authors opinion justify routine use of streptomycin

Result in 15 patients with disseminated nodular tuberculosis confirm experience of others that streptomycin is of great value

[This experience is interesting since it demonstrates that not all chronic lesions are of a caseous and fibrotic character and irreversible The corollary is that some patients with the chronic disease may be prepared with streptomycin for surgery or other procedures designed to treat cavities and other irreparable damage —Ed]

Role of Pulmonary Cavitation in Development of Bacterial Resistance to Streptomycin Using growth in 10 μg streptomycin ml as the criterion for resistance W L Howard E E Mueller S A Yannitelli and C F Woodruff[2] (Detroit Mun Tuberculosis Sanatorium) studied 89 patients with cavitation 37 with equivocal findings and 41 without cavity Of those with cavitation 84 1 per cent produced resistant tubercle bacilli among cultures obtained 28-41 days after beginning of therapy 58 3 per cent were resistant after 42 83 days 90 per cent were resistant and after 84 days all were resistant

Among patients who had completed therapy but in whom cavitation was equivocal resistant strains of

(2) Am Rev T b 59 391 47) Ap l 19 9



F g 33 (t p) —Lower h lf f l ft l g b f t pt my n t tm t
F g 34 (bo t m) —L w half f l ft l ng t nd f st pt my n t e tm nt
(Cou t y f Howl tt K S J d O C J L Am R T b c 58 139 172 Aug st 1948)

20 mg/kg body weight daily for 45 days) resistant strains developed in 13 of 47 patients Resistance occurred in 33 of 56 patients with frank caseation or cavity but did not occur in any of 31 patients without such lesions

Data from this and other studies have suggested that emergence of resistant strains was influenced far more by duration than by daily dose of streptomycin It must be concluded that reduction of therapy from 120 to 42 or 45 days has been much less successful than had been hoped There is limited evidence in this study to suggest that if tubercle bacilli are sensitive to streptomycin when sputum conversion occurs they are likely to remain so Sensitivity must be regarded as indeterminate until the effects of the entire course of streptomycin is known

The relationship between type of tuberculosis being treated and incidence of resistant tubercle bacilli is too close to be the result of chance However patients without frank caseation or demonstrable cavity are not necessarily immune to emergence of drug resistant strains although the number in which this will happen will be small Presence of frank caseation or a cavity has already influenced greatly the therapeutic results obtained from streptomycin and it is not unreasonable that incidence of resistant bacilli should also be influenced

Follow up of patients treated at this sanatorium showed that when treatment by bed rest has failed streptomycin alone is unlikely to produce sustained arrest of frankly caseous or cavernous pulmonary tuberculosis In such cases optimal results can be achieved only by integration of streptomycin with appropriate forms of collapse resection or other surgery

Experimental and Clinical Studies of Role of Streptomycin in Pleural Cavity Since the beneficial effects of streptomycin on human tuberculosis have been demonstrated it is reasonable to assume that local use of streptomycin in the human pleura for tuberculous effusions or tuberculous empyema might be desirable Moreover

bacilli developed in 10 8 per cent In only two patients without cavities did resistant organisms develop and six still harbored bacilli sensitive to 1 μg streptomycin after 84 or more days treatment

In the presence of persistent cavitation development of resistant strains is significant but if cavitation is not present or is equivocal at the end of treatment it is not Because of rarity of resistant bacilli in persons without cavitation the fear that they might harbor highly resistant organisms in some obscure focus seems unfounded

There are several reasons for the importance of a cavity in determining whether or not resistance will develop Organisms grow much more rapidly in cavities where they have been exteriorized as far as the ordinary body defense mechanisms are concerned and rapid multiplication is generally accepted as important in the development of resistant micro organisms The relatively avascular walls of older chronic tuberculous cavities militate against streptomycin s reaching the interior in effective concentrations The opportunity for the tubercle bacillus to grow in fluid or semifluid medium in the cavity instead of on the surface of cells may be important in development of highly resistant strains

Streptomycin given in a single dose of 1 Gm on alternate days might be more effective than 0 5 Gm given daily With such a method cumulative toxicity of long continued daily doses of streptomycin may be avoided while an effective attack against the bacillus is maintained Smaller doses have not prevented rapid emergence of highly resistant strains

Sensitivity of Tubercle Bacilli to Streptomycin Influence of Various Factors on Emergence of Resistant Strains Among 28 patients treated on regimens of 1 8 or 2 0 Gm streptomycin daily for 120 days by Kirby S Howlett Jr John B O Connor Joseph F Sadusk Jr William F Swift Jr and Frederick A Beardsley [3] resistant strains of tubercle bacilli developed in 8 When on a regimen of 1 0 Gm daily for 42 days (later revised to

(3) Am Rev Tub 59 40 414 April 1949

the toxicity of a crude preparation of dihydrostreptomycin assaying 0 34 0 57 Gm active base /Gm solid material and a purified preparation assaying 0 75 Gm base /Gm solid with that of streptomycin Pharmacologic and antibacterial characteristics of streptomycin and dihydrostreptomycin are qualitatively similar but certain quantitative differences between the compounds may be important Most important toxic reactions produced by streptomycin can be produced by the dihydro derivative In 5 Gm daily doses for 30 days or longer dihydrostreptomycin caused vestibular dysfunction hearing loss renal damage and eosinophilia Neurotoxicity as indicated by the appearance of dizziness characteristic of vestibular dysfunction is manifested later and after a larger total dose with 5 Gm dihydrostreptomycin daily than with 3 Gm streptomycin daily

Dihydrostreptomycin can also produce damage to auditory apparatus and although comparison is difficult observation indicates that it may be no more toxic and may be significantly less toxic in this respect than streptomycin The three patients in this study who showed renal damage received very large doses of the crude dihydrostreptomycin preparation Renal toxicity of the large amounts of impurities received is unknown No evidence of renal dysfunction was observed with 3 Gm or less dihydrostreptomycin daily Crude preparations frequently caused severe local reactions at the site of injection but purified preparations did not

Dihydrostreptomycin in doses as high as 2 Gm daily was tolerated without untoward reaction by five patients with readily demonstrable hypersensitivity to streptomycin The new drug should be given patients with this type of reaction when interruption of treatment is undesirable In five patients every strain of Mycobacterium tuberculosis which was highly resistant to 1 000 μg/cc of one compound was resistant to the other Strains inhibited by low concentrations of streptomycin were also inhibited by low concentrations of dihydro treptomycin

In 12 tuberculous patients treated with dihydrostrepto

local use of the antibiotic after pulmonary resections for tuberculosis could be expected to reduce incidence of tuberculous empyema Edward J Beattie Jr Brian Blades and Charles Horton[4] (George Washington Univ) attempted to determine whether or not streptomycin injected into the pleural cavity produced deleterious effects on the pleura serosa and to determine absorption rate of streptomycin from the pleural cavity

TECHNIC —In nine apparently healthy dogs the left or right pleural cavity was entered by resecting a 4 cm long piece of rib Isotonic saline 100 cc was placed in pleural cavities of three dogs Isotonic saline 100 cc containing 0 5 Gm streptomycin (calcium chloride complex) was placed in pleural cavities of six dogs The seventh postoperative day wounds were reopened and biopsies taken both from the pleura involved in the scar and from pleura away from the scar

In 12 human patients 0 5 Gm streptomycin in 10 cc saline and 100 000 units of penicillin in 10 cc saline were instilled in the pleural cavity at the close of thoracotomy Streptomycin assay studies were carried out on pleural fluid and venous blood of both dogs and patients

Absorption rate of streptomycin from the dogs pleuras was rapid and maximal blood levels were reached in 30 60 minutes There were no apparent differences in the microscopic picture of the pleura from animals receiving saline and animals receiving streptomycin

Of the 12 human patients 6 were considered to have unscarred pleuras whereas in 2 the pleura was moderately scarred and in 4 it was markedly scarred Absorption curves were similar in all three types Absorption is rapid usually being maximal in 30 minutes and the level falling low in 6-8 hours

[Instillation of streptomycin into the pleural cavity has not proved effective in tuberculous empyema Other local chemotherapy will undoubtedly be investigated —Ed]

Laboratory and Clinical Investigation of Dihydro streptomycin, an antibacterial agent prepared by catalytic hydrogenation of streptomycin is reported by Lawrence B Hobson Ralph Tompsett Carl Muschenheim and Walsh McDermott[5] (Cornell Univ) They compared

(4) J Thoracic Surg 18 535 Feb 1949
(5) Am Rev Tuberc 58 501 514 Nov 1948

others during the sixth month of treatment Results suggest that combined therapy may delay emergence of streptomycin resistant strains of tubercle bacilli

[Great interest is now centered on the combined use of streptomycin and para aminosalicylic acid While their combination may not be followed by early development of resistance to either evidence is beginning to accumulate that resistance may develop eventually to both drugs However the advantage of postponement of resistance i obvious since it is so desirable in many cases to administer treatment over a prolonged period (four to six months or even longer) to promote lasting arrest of the disease processes —Ed]

Treatment of Experimental Tuberculosis in Mice and Guinea Pigs with Para aminosalicylic Acid (PAS) and Streptomycin B Swedberg and G Widstrom[7] (Stockholm) in in vitro experiments found no sharp boundary between the concentration of PAS which arrests growth of tubercle bacilli and that permitting growth Different strains varied considerably in primary susceptibility to PAS As length of the experiment was extended tubercle bacilli grew in increasing concentrations of this substance

When administered to mice or guinea pigs into which had been injected PAS susceptible H37 strain of tubercle bacillus or PAS resistant Ravenel strain PAS had an effect that was not always significant In similar animal experiments streptomycin showed considerable effect against both strains Further experiments showed that the combined effect of PAS and streptomycin was not greater than that of either drug alone

The results confirmed those of Youmans who found that PAS was moderately effective for suppression of tuberculosis infection in white mice but not as effective as streptomycin

[Bloch (Am Rev Tuberc 59 554 561 May 1949) on the contrary reports that the combination of these drugs has a much more favorable effect in experimental tuberculosis in guinea pigs than either drug used alone —Ed]

Para aminosalicylic Acid (PAS) Treatment of Tuberculosis with Special Consideration of Bronchial and Renal Tuberculosis R Hug S Moeschlin and E Tan

(7) A t m 1 Sea d 131 116 1 8 1948

mycin changes in the course during treatment seemed at least as marked as those previously observed from streptomycin administration

The precise relation of toxic doses to optimal therapeutic doses of streptomycin has not been established It is important that experience be gained on therapeutic effectiveness of dihydrostreptomycin in dosages well tolerated for long periods The dihydro derivative is preferable to streptomycin for prolonged treatment of patients requiring large doses or long courses

[This is one of six articles on dihydro treptomycin in the November issue of the *American Review of Tuberculosis* All bear out the observation that dihydrostreptomycin is less toxic than streptomycin although this is only a matter of degree and therefore that the drug might be us d in higher do ag it desired. There have been reports of deafness appearing some months after the use of dihydrostreptomycin but most experience casts doubt on the relation of this deafn ss to the drug Dihydrostreptomycin seems to be as effective as streptomycin but is not active against strains of tubercle bacillus which are resistant to streptomycin —Ed]

Effect of Combined Therapy with Streptomycin, Para aminosalicylic Acid and Promin® on Emergence of Streptomycin Resistant Strains of Tubercle Bacilli Preliminary Report Alfred G Karlson Karl H Pfeutze David T Carr William H Feldman and H Corwin Hinshaw[6] gave the drugs in various combinations to 14 patients with tuberculosis who were expected to discharge tubercle bacilli so that the organism s sensitivity to streptomycin might be determined periodically Streptomycin was administered intramuscularly twice daily in 0 5 Gm doses to five patients and 0 5 Gm was given once daily to the others Para aminosalicylic acid dosage *varied from 5 to 10 Gm /day and 5 Gm promin®* was administered intravenously for the first 14 days of each 21 day period There was no evidence that administration of more than one of the drugs at a time increased their toxicity After three months therapy streptomycin resistant tubercle bacilli had been demonstrated in only 1 patient of the 12 from whom the organisms could be cultured Resistant strains were demonstrated in three

(6) P oc Staff M t M y Cl n 24 85 88 F b 16 194

The authors used the drug in 49 patients with pulmonary tuberculosis observed 2 10 months Especially in patients with toxic exudative lesions the general condition improved after a short time cough and expectoration decreased and in a few weeks the bacilli became scarcer and even disappeared After two or more months of PAS treatment the previously stationary roentgen picture improved in some

Five patients with exudative pleuritis given 12 14 Gm of the drug daily seemed to show no convincing difference from responses in controls

[Since the sodium salt of PAS is reported to be ex reted more rapidly than PAS there seem to be a rea on for u ing the latter When given after meals and di solved in milk or other fluid it is t lerated by most patient without gastrointest nal irritation Alm and H lander (Acta tuberc Scandinav 22 283 287 1948) report i teresting fluorescence m cro copic studies showing that PAS accumulates in elastic fiber and that a normal lung absorb relatively large quant t e —Ed]

Chemotherapy of Tuberculosis with Para aminosalicylic Acid Since March 1948 H Steinlin and E Wilhelmi[9] *(Heiligenschwendi) have treated 106 patients* with aminacyl® Wander (para aminosalicylic acid PAS) 53 orally 37 locally and 16 by both method Of the 69 orally treated patients results in 50 aged 15 58 are discussed here Treatment lasted two to seven months and 24 received aminacyl® only and 26 were given streptomycin concurrently Severe cases predominated In the beginning 15 cc of a 20 per cent solution of the sodium salt was administered five times daily but its bitter salty taste was objectionable 0 5 Gm tablets were more palatable but often caused gastric di turbances Lately the sodium salt 0 34 Gm corresponding to 0 3 Gm free acid has been given exclusively Ten capsules are taken five times daily and gastrointestinal upsets are slight and infrequent The drug is given on four successive days followed by three days rest In renal tuberculosis daily dose is 6 9 Gm PAS in 6 8 week courses interrupted by 8 14 days rest In general PAS must be given orally for at least four to six months In

(9) S h m d W h b 8 1 1912 4 D 18 1948

ner[9] (Zurich) treated five patients with tracheobronchial tuberculosis by oral administration of 12 15 Gm of PAS daily divided into five equal doses given mostly for four days followed by a rest of four days Some patients have been given the drug for six day periods interrupted by rests of two to four days Less frequently the drug has been administered continuously as done in Sweden Healing or noticeable improvement was obtained in two patients who had not received previous treatment In two others who had received repeated streptomycin treat ment with only partial regression of the ulcerating proc ess PAS produced surprising improvement in one and provisional clinical healing in the other In the remain ing patient who had a severe recurrence after suspension of streptomycin treatment PAS healed the recurring lesion On the basis of their experience the authors think that PAS therapy is indicated at least in patients in whom streptomycin has not healed tuberculous ulcera tions of the tracheobronchial mucosa

The authors have used PAS in 12 cases of renal tuber culosis 5 were unilateral 1 bilateral and 6 involved re maining diseased kidneys after nephrectomy on the opposite side All patients had descending tuberculosis of the bladder and in eight the prostate and epididymi were also involved Dosage was 12 14 Gm daily by mouth In addition to a questionable effect on the tuber culous renal process itself PAS has a favorable influ ence on associated involvement of the urinary passage Recent tuberculous processes of the bladder heal prompt ly older processes react more slowly and not as well although the subjective symptoms are generally decided ly improved In three patients with decreased renal function uremia occurred during PAS treatment a com plication which could only be avoided by decreasing the dosage of the drug to 4 Gm daily Regular determina tion of the urea level in the serum of patients with reduced renal function is therefore necessary if uremia is to be avoided

(8) S l med W h sch 79 353 357 Ap 23

A 10 per cent solution of aminacyl® was used in local treatment of 47 pleural empyemas and effusions In pa tients with pulmonary fistula who cough up part of the empyema and in fresh pleuritis with effusion a 5 per cent solution was used to avoid irritation Of 30 patients with bacillus positive smears or cultures 26 became negative in one to five months and 4 remained positive 8 effusions dried up and in about half the patients the empyema became more fluid and even serous clear in some Many empyemas were bacillus free after two to four injections

In four patients 2 10 cc of a 5 per cent solution was injected into a cavity and in four other patients strepto mycin was similarly injected the cavities decreased in size in both groups A fistula that had been treated un successfully with streptomycin for several months closed after aminacyl® treatment of four week Tuberculous lymph nodes of the neck decreased in size after injection of a 4 per cent solution concentrations of 10 per cent may be used in older gland abscesses Two patients with ulcerated skin tuberculosis treated with aminacyl® oint ment and powder show good healing tendency

Various new chemotherapeutic agent are being reported and tested and the following articl s record some early re ults

Waksman and Lechevalier (Science 109 305 39/ Mar h 25 1949) have repo ted the di covery of neomycin This i effective experimentally against the tubercle bacillus including strains re sistant to str ptomy in It toxicity i under investigation and no clinical reports have yet appeared

The activity of new sulfon combinations is al o under investiga tion These include cilag® (sulfon N ac tate) and sulfetrone®

Aureomycin exl it t some activity in vitro again t the tubercle bacillus but was not found by Steenken and Wolin ky (Am Rev Tuberc 59 2 1 February 1949) to have any favorable effect against guinea pig tuberculosis Similarly Steinbach and hi associates (Am Rev Tuberc 59 6 4 631 June 1949) did not observe any clinical effects in three young adult patients with acute extensive exudative forms of pulmonary tubercul sis —Ed

Treatment of Tuberculosis with Sulfetrone® D G Madigan[1] (Farnborough Kent) reports experience in 70 cases since 1943 Most patients had pulmonary disease All were given 3 Gm ferrous sulfate orally three times

(1) La t 2 174 179 J 1 31 1948

contrast to streptomycin aminacyl® caused no neurologic or cutaneous disturbances

In the beginning blood was examined every eight days in about 300 specimens no toxic changes shifts to the left or eosinophilia were observed The eosinophilia caused by streptomycin was not influenced by aminacyl® Red cell count was normal but leukocyte count was often somewhat increased Blood level of free and total PAS showed great individual variations ranging between 2 and 16 mg per cent when 40 capsules daily were ingested Renal elimination of the drug like that of penicillin is mostly by tubular excretion and therefore rapid

The first and most convincing effect of the drug is a fall in temperature by lysis without increased perspiration Pulse usually becomes slower and more constant

Sedimentation rate which was above normal in 20 of 24 patients decreased in 14 and remained the same in 6 Hemoglobin level increased in 19 and remained the same in 5 No hemoglobin level fell below 60 per cent Cough stopped in nearly all cases Sputum of 17 patients was positive it became negative in 12 and remained positive in 5 (3 of these had been treated for only two to three months and the other 2 had large cavities)

Body weight increased in 17 patients remained the same in 3 and decreased in 4 1 of whom was overweight General condition improved in 18 remained the same in 4 and deteriorated in 2

One patient died after cavity perforation with pressure pneumothorax but aminacyl® had improved his general condition before the accident

Lung x rays of patients treated four to seven months showed improvement in nine no change in three and aggravation in one

Patients simultaneously treated with streptomycin and aminacyl® received 0 5 Gm streptomycin twice daily for a total dose of about 100 Gm The impression was that the combined treatment was superior to treatment with either drug alone

[The therapeutics and toxicology of this drug a complicated sulfone have been described by Brownlie (Lancet 255 131 134 July 4 1948) Other clinical reports have also appeared in the Lancet —Ed]

Effect of Nicotinic Acid Amide on Experimental Tuberculosis of White Mice To test the therapeutic effect of various chemicals D McKenzie L Malone S Kushner J J Oleson and Y SubbaRow (Pearl River N Y) infected Swiss mice by intravenous administration of 0 25 mg of a tubercle bacillus suspension ($H_3 Rv$) Animals so infected and left untreated usually died in 3 3½ weeks The disease seemed to be centered mainly in the lungs other organs being only slightly involved Usually oral treatment of infected animals was begun the day after inoculation

Of the pyridine carboxylic acid compounds nicotinamide was the most active tested Administration of 0 5 0 75 per cent of this substance in the diet markedly suppressed spread of tuberculosis in the infected animals Its effect roughly paralleled that of 1 mg streptomycin given four times daily over the same period

The dose for human beings if calculated on a weight basis from the results in mice could not be tolerated All changes introduced into the nicotinic acid amide molecule either increased the toxicity or reduced the activity or both Riboflavin seemed to have a slight effect in reducing the total treatment dose of the nicotinic acid amide Tubercle bacilli showed some evidence of resistance to this substance after five mouse passages

Significance of Positive Cultures in Apparently Adequately Treated Patients with Pulmonary Tuberculosis Hans Abeles[3] (New York City) studied record of 199 patients with arrested or apparently arrested tuberculosis discharged in a three year period to determine prognostic significance of occasional tubercle bacilli in sputum All patients had at least two cultures including at least one gastric culture in the six months before discharge During this period concentrated specimens of sputum

( ) J L I & Cl M d 33 1 49 1 53 O t be 1948
(3) A R T be 5 8 313 S ptembe 194

daily and 2 drachms fresh brewers yeast daily for two weeks before and throughout sulfetrone® therapy to offset hypochromic and nutritional anemias caused by the drug A third form hemolytic anemia develops and continues throughout administration of sulfetrone® and may be responsible for reduction of hemoglobin to a level as low as 60 per cent Should hemoglobin fall below this level the drug must be withdrawn Blood sulfetrone® concentrations of 7 5 10 mg/100 ml were aimed at Massive initial doses were not well tolerated so dose were gradually increased beginning with 1 5 Gm daily the first week and increasing by 1 2 Gm each week until desired blood levels were attained Weekly checks of red cells hemoglobin and blood sulfetrone® levels were made Duration of therapy varied from a few days in tuberculous meningitis to 18 months in chronic cases

Minor toxic manifestations of sulfetrone® therapy were slight headache difficulty in reading and concentration temporary depression and nausea and cyanosis of skin and mucosa and required no treatment other than reassurance Moderate or severe continuous headache loss of appetite vomiting gastrointestinal discomfort dizziness and mental confusion were considered dangerous and were associated with blood sulfetrone® levels above 12 15 mg/100 ml Such symptoms were treated by measures that would hasten elimination of the drug

In general no beneficial effect was detected from such therapy in acute infections i e acute miliary tuberculosis and tuberculous meningitis but a patient with chronic miliary tuberculosis recovered Improvement was observed in chronic lesions thus 12 of 17 patients with acute pulmonary fibrocaseous disease and 13 of 22 with chronic cases improved All four patients with primary pulmonary tuberculosis and six of eight with strictly exudative lesions improved All four in the chronic hematogenous group and three of four in the productive pulmonary infiltrative group improved In general all exudative phases of infiltrative disease were halted and reversed by sulfetrone®

sidered to have occasional positive sputum Smears only were made for 243 hospitalized and discharged before June 1935 Patients were divided into three groups A those with consistently negative sputum cultures during the last six months of hospitalization B those with occasionally positive sputum cultures and C the 243 patients discharged before June 1935 with consistently negative sputum smears

Recurrence rates of patients in group A were much lower than those in groups B and C Among patients followed four or more years after discharge who had minimal tuberculosis recurrence rate in group A was 11 per cent in group B 21 per cent and in group C 21 per cent Among those with moderately advanced lesions followed four years or more reactivation rate was 20 per cent in group A 32 per cent in group B and 38 per cent in group C Among patients in far advanced stages followed for this period reactivation rate in group A was 27 per cent in group B 52 per cent and in group C 57 per cent

It seems likely that sputum cultures done before June 1935 would have revealed tubercle bacilli in sputum of patients whose smears were negative

Phrenic Nerve Interruption in Treatment of Pulmonary Tuberculosis Statistical Analysis of Results in 398 Patients at Trudeau Sanatorium from 1925 through November 1947 Roger S Mitchell found data on only 292 patients adequate for detailed study Age range was 15 56 59 per cent of patients were 26-40 About a third of permanent interruptions were initially successful and the gain was maintained in one fifth of the cases whereas about half the temporary interruptions yielded good immediate results and about a third good final results Cumulative relapse rate after initial good results in 117 patients followed five or more years was 40 per cent

The 221 patients with moderately advanced disease (standard National Tuberculosis Association classification) responded much more favorably than the 69 with

(5) Am R T be 58 619 64 Dec mbe 1948

were examined at least once a month Among 199 patients 104 had consistently negative cultures during the specified period and the remaining 95 had one or more positive cultures Frequently only single positive cultures were obtained Extent of disease and duration of observation after discharge were approximately the same for the two groups During an observation period averaging 29 months 36 patients were readmitted Of these 25 had had occasional positive cultures before discharge and 11 had had consistently negative cultures After four years the cumulative rate of readmitted patients discharged with positive cultures was 28 5 per cent and of readmitted patients discharged with negative cultures 10 5 per cent The immediate reason for readmission was progression of serial roentgenograms in all 11 patients discharged with negative cultures and in 21 of those who had had occasional positive cultures Reason for readmission of the other four who had had occasional positive cultures was recurrence of positive sputum

Abeles suggests that positive cultures of gastric contents might have been found in some patients with consistently negative sputum cultures

[Relapse of pulmonary tuberculosis is almost always explained by the mechanism of bronchogenic spread of the infection from a cavity which has never healed or one which has partly healed and broken down A positive culture or an occasional positive sputum is synonymous with an ulcerated or excavated lesion and thus should always be regarded as a possible source of progressive disease—Ed]

Prognostic Significance of Occasionally Positive Sputum after Adequate Treatment of Tuberculosis Follow up Study of Discharged Patients Robert Chang[4] (Massachusetts Dept of Health) analyzed records of 864 patients discharged from the Rutland State Sanatorium with arrested or apparently arrested tuberculosis to determine if occasional positive sputa during the last six months of hospitalization have prognostic significance Of 621 patients discharged after June 1935 all had at least six cultures of 24 72 hour specimens of sputa If one or two of these were positive the patient was con

(4) Am Rev Tuberc 58 303 307 September 194

the hemidiaphragm has surprisingly little effect on results of phrenic nerve interruption

Question of Treating Primary Tuberculous Pleurisy with Preventive Artificial Pneumothorax Olof de Mare[6] reviewed records of 562 patients with pleurisy to determine the advisability of using therapeutic pneumothorax to prevent development of pulmonary tuberculosis Homolateral pulmonary tuberculosis develops in about one tenth of patients with primary pleurisy Comparison of patients treated with and those treated without pneumothorax showed no statistically significant difference in the tendency to progressive pulmonary tuberculosis There was however some indication that morbidity of pulmonary tuberculosis in patients with pleurisy and perceptible homolateral tuberculosis was less in those treated with pneumothorax

Great difficulty was experienced in maintaining pneumothorax For various reasons it was necessary to abandon this treatment in 86 patients within one year and in 7 others within three years Extension of adhesions in these patients was less dependent on the interval between onset of pleurisy and initiation of pneumothorax than on the nature of the pleurisy Intensity of pleural thickening depended chiefly on volume of exudate Risk of empyema was somewhat greater in patients treated with pneumothorax than in those not so treated but was not great in either group

De Mare concludes that general use of pneumothorax in patients with pleurisy is unjustified but that when homolateral parenchymal changes or great hilar adenitis complicates pleurisy therapeutic pneumothorax should be attempted Patients with pleurisy and effusion should be hospitalized Those with small volumes of exudate which do not prevent evaluation of lung parenchyma need not be tapped if parenchymal changes are excluded otherwise thoracentesis should be performed and therapeutic pneumothorax maintained until active homolateral changes can be excluded by x ray examination and cul

(6) A ta t b S d 2 15 196 1948

far advanced disease Two had minimal disease and good results Disease showing distinct improvement under observation responded much better than relatively static disease and still better than that which was getting distinctly worse before operation Initial and final results were poor with old well established disease Location of lesions in the lungs had little influence on results Improvement was striking when cavities were less than 2 cm in diameter Thin walled cavities responded best but there were 24 per cent final good results with the thick walled variety The denser the x ray shadows except of cavity walls the poorer the results Cavitation in contralateral lung was likely to be associated with homolateral failure but final good results were apparently unaffected by extent or activity of disease in the contralateral lung in absence of cavity After three months contralateral disease was apt to deteriorate except when it was ancient and arrested but when no disease was present at the time of operation spread was not seen

When the hemidiaphragm showed elevation two posterior interspaces or more above its preoperative level on full inspiration initial good results in 38 patients were higher (66 per cent) than for any other factor studied and relapse rate was negligible Mean postoperative sanatorium residence of 90 patients with final good results was 10 months

Review of serial preoperative x rays of patients with unpredictably good results frequently revealed progressive retraction of the diseased portion of lung as evidenced by strandlike shadows radiating from the hilus and retraction of mediastinal structures ribs and hemidiaphragm This finding was infrequent in patients with unaccountably poor results Respiratory distress and obstructive endobronchial tuberculosis were regarded as contraindications to the procedure

Phreniclasis may be repeated as often as necessary to maintain a therapeutically successful hemidiaphragmatic paralysis for 12 18 months Preoperative immobility of

A pleural tear will cause pneumothorax which may be used effectively

On the first postoperative day the chest is fluoroscoped or a bedside x ray is made Fluid usually present should be aspirated and replaced by air Irrigation with sterile normal saline is started at the same time to prevent clot formation in the extrapleural space After aspiration and irrigation sulfadiazine or penicillin may be left in the space to prevent extrapleural empyema Aspiration irrigation and air replacement are repeated at 48 hour intervals until fluid balance becomes stabilized usually between 5 and 10 days after operation In 7 14 days after operation the patient is transferred to a sanatorium where collapse is maintained by suitable fills of air semiweekly and then weekly If space is not dry in four to eight weeks tuberculous and/or nontuberculous extrapleural empyema should be suspected Both respond well to treatment and are not regarded with alarm Broncho extrapleural fistula is suggested by sudden appearance of purulent sputum noticeable pulmonary compression or inability to obtain usual positive pressure Methylene blue instilled into the space will appear in sputum Nontuberculous empyema is treated by aspiration lavage with normal saline air replacement and use of antibiotics Three or four such treatments are usually sufficient Tuberculous empyema is treated by aspiration lavage with 15 20 cc of 2 per cent methylene blue in 95 per cent alcohol every three or four days with air replacement until pus production is minimized Then oil is gradually substituted for air

Oleothorax maintains collapse and retards pus formation Inferior limits of extrapleural space should be firmly adherent before oil is used and bronchial fistulas should not be present Initial fill of 30 50 cc sterile mineral oil of neutral pH and no 5 viscosity is used Entire conversion lasts three to six weeks never more than 400 cc oil is used for any one space Patients are re examined every three to six months If extrapleural pressure is too great or too little a sensation of tightness is experi

ture of sputum or gastric lavage If examination results are negative pneumothorax should be abandoned if they are positive it should be maintained for two or three years if possible High fever and extensive exudate or prolonged elevation of sedimentation rate suggests even more strongly the need for pneumothorax

[There are many objections to use of pneumothorax for simple pleurisy with effusion Duration of the pleurisy is likely to be prolonged because of interference with the actual healing process and there is a possibility that organization of the pleura over the collapsed lung will seriously interfere with its later re expansion and proper function —Ed]

Extrapleural Pneumothorax Five Year Study Elliott P Smart Paul C Samson and Max E Childress[7] evaluated results of extrapleural pneumothorax induced in 45 patients during a four year period Indications for extrapleural pneumothorax are indefinite The authors attempt either thoracoplasty or extrapleural pneumothorax in patients in whom intrapleural pneumothorax is unsuccessful If the lesion is more exudative than productive extrapleural pneumothorax is preferred if the lesion is more productive than exudative thoracoplasty is used Extrapleural pneumothorax is not used in large peripherally located cavities tension cavities or acute ulcerative tracheobronchitis Although the operation is not used to prepare for later thoracoplasty thoracoplasty can be used if extrapleural pneumothorax fails

TECHNIC —Through a curved incision over the fourth intercostal space from the edge of the erector spinae muscle to the inferior angle of the forward drawn scapula 10 cm of the fourth rib is resected subperiosteally and after excision of muscle fibers the parietal pleura is stripped from the deep periosteum by blunt dissection exposing the seventh rib posteriorly fifth rib laterally third rib anteriorly azygous vein on the right and the midaortic arch on the left This constitutes circumferential collapse of the apex carried to the hilus of the lung with edges curved slightly downward giving the appearance of a flattened dome The wound is closed and an 18 gauge needle inserted through the second anterior intercostal space in the midclavicular line extrapleural pressure is adjusted to atmospheric or slightly positive Hemorrhage is usually easily controlled but may necessitate resection of an additional rib

( ) Am R T be 58 34 J ly 1948

A pleural tear will cause pneumothorax which may be used effectively

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enced and oil pressure is readjusted If oil is expectorated or if an extrapleural cutaneous fistula forms oil is removed otherwise it is left indefinitely Usual indications for extrapleural oleothorax are tuberculous *extrapleural empyema and forestalling obliterative processes* in the extrapleural space

Of 52 extrapleural pneumothoraxes induced in 45 patients 39 operations were completely satisfactory in that disease of adjacent lung was controlled Of the 45 31 were working five years after operation 1 was convalescent condition of 2 was unknown and 11 had died At this time 17 patients had extrapleural oleothorax the extrapleural space had been obliterated in 13 had not been obliterated in 2 thoracoplasty had been performed in 3 and status of 3 was not known

[This procedure is generally used in some clinics particularly in France and Switzerland Most American surgeons prefer thoracoplasty even though a preliminary period of rest treatment may be necessary to condition the patient and his disease for this procedure —E I]

Lobectomy and Pneumonectomy in Pulmonary Tuberculosis According to Herbert C Maier [8] pulmonary resection is indicated for patients with tuberculosis when adequate thoracoplasty has failed to produce cavity closure and convert sputum provided more than an occasional sputum culture or gastric concentrate has yielded tubercle bacilli When stenosis of a *main bronchus* or a lobar branch bronchus is present *and if streptomycin* is required to control the bronchial lesion resection should be seriously considered while the beneficial effect of streptomycin is present Patients with bronchiectasis secondary to pulmonary tuberculosis and symptoms especially recurrent hemoptysis due to bronchial infection are best treated surgically Primary lobectomy is preferable to thoracoplasty when cavities are in the basal portion of the lower lobe and the active tuberculous process is limited to lower or middle and lower lobes More conservative procedures may be given a trial if bronchial involvement is slight Lower lobe apical cavities may be

(8) Am R T be 58 5 6-5 8 N mbe 19

closed by thoracoplasty but involvement in the adjacent lower part of the upper lobe usually requires pneumonectomy Tuberculomas are an indication for partial or total lobectomy There is considerable difference of opinion concerning advisability of pulmonary resection for treatment of tension cavities A trial with thoracoplasty without streptomycin is indicated in some cases The response of tension cavities to collapse procedures is unpredictable Antibiotics should be reserved for resection if the latter is required Relative merits of thoracoplasty and pneumonectomy in extensive unilateral tuberculosis have been debated at length Although cavity closure and sputum conversion after thoracoplasty may occur infrequently the patient s general condition may improve and diminution in amount in infectivity of sputum may follow Pulmonary resection if then necessary can be performed without much difference in operative risk Some patients may obtain such a satisfactory result from thoracoplasty that no further surgery is required If there is doubt as to whether thoracoplasty will be adequate streptomycin should be withheld in order to avoid pulmonary resection on a patient with tubercle bacilli resistant to streptomycin If no major surgical procedure can be undertaken without streptomycin and there is considerable chance that pneumonectomy will be required resection should be done at once while maximal effect of streptomycin is obtainable

Overdistention of remaining pulmonary tissue following either lobectomy or pneumonectomy in tuberculous patients is disadvantageous and thoracoplasty should be performed soon after resection An exception should be made for patients in the growing age

Use of streptomycin has necessitated re evaluation of the status of pulmonary resection in tuberculosis Although operative morbidity and mortality have been considerably reduced the effect on late exacerbations of streptomycin in the operative period has not been finally assessed

Immunologically resection does not seem more bene

ficial than collapse At present lobectomy and pneumonectomy should be restricted to cases in which collapse therapy is inadequate

[The indications for such pulmonary resections are still unclear and careful judgment must be used in every ca e without adhering closely to a set rule It is a great mistake to assume that pulmonary tuberculosis can ever be completely resected After undergoing such a erious procedure the patient should be kept on the rest cure in order to gain the most from the sacrifice of tissue —Ed]

Thoracoplasty in Treatment of Pulmonary Tuberculosis Analysis of Results 5 26 Years after Operation is presented by T J Kinsella E S Mariette P M Matill E P K Fenger V K Funk L M Larson S S Cohen and F C Nemec[9] (Glen Lake Sanatorium Oak Terrace Minn) Between 1922 and 1943 unilateral thoracoplasty was performed in 1 562 operations on 609 patients 4 patients had bilateral thoracoplasty performed in 12 operations At time of surgery 12 1 per cent had unilateral disease and 87 9 per cent bilateral The good chronic was preferred for surgical treatment and most patients had thoracoplasty because of cavitation or persistence of phenomena arising from cavities such as continued cough with discharge of tubercle bacilli or pulmonary hemorrhage A smaller group was operated on becau e of primary pyothorax or pyopneumothorax complicating previous artificial pneumothorax In most patients artificial pneumothorax had either failed or proved unsatisfactory Operation was performed because of far advanced disease in 383 moderately advanced disease in 229 and minimal disease in 1

Within eight weeks of operation 34 patients died a mortality rate of 5 55 per cent/patient or 2 16 per cent/operation The eight weeks operative mortality since 1931 has been 3 per cent/patient and 1 16 per cent/operation

Spread of tuberculosis was encountered 94 times in 90 patients a rate of 14 66 per cent/patient or 6 34 per cent/operation In 34 spread occurred to areas not previously involved and in only 10 half of whom had ipso

(9) Am R Tub r 59 111 1 7 F bru y 1949

lateral diaphragm paralysis at the time of surgery was spread on the same side as thoracoplasty All of five patients with pyopneumothorax in whom spread developed had a bronchial fistula at time of surgery In 39 who died within two years postoperatively spread was definitely a causative factor

Of the 613 patients 410 (66 8 per cent) survived 5 26 years after surgery With those who died from causes unrelated to tuberculosis deducted mortality rate was 27 57 per cent In 141 patients with cavities over 4 cm in diameter closure was obtained in 49 6 per cent and sputum became negative for bacilli in 76 5 per cent In 317 with small cavities these closed in 68 7 per cent and sputum conversion occurred in 90 95 per cent Empyema pocket was obliterated in 61 of 94 who had pyopneumothorax Of the 94 12 died within one year of operation

[This l ng follow up provides a good basis for estimating what may be exp cte l of thoracoplasty carried out in well elected ases by good surgeons under favorable conditions —Ed]

Incidence of Pulmonary Tuberculous 'Spreads' Following Thoracic Surgery and Anesthesia William M Parke Jr Edward R Loftus and Harold F Bishop[1] (Valhalla N Y) review the incidence of spread following 805 anesthetic administrations for thoracic surgery in treatment of pulmonary tuberculosis in 367 patients All the procedures were done on patients with active moderately or far advanced cavitary disease Various stages of thoracoplasty were performed in 755 instances The remaining 50 operations included lobectomies cavernostomies thoracotomie and extrapleural pneumothorax Criterion for spread of the disease in the lung was x ray evidence of an infiltration that persisted or progressed over at least a month postoperatively

Various degrees of spread followed 81 procedures (10 per cent) There was slight but definite evidence of dissemination in 19 instances Twenty eight extensions were of major proportions Incidence of spread in patients with positive sputum was 12 per cent and in those with negative sputum 3 6 per cent Spread occurred

(1) N w Y k St t J M d 48 1685 1687 A g 1 1948

about twice as frequently in Negroes as in white patients

Regional or local anesthesia without supplementary general anesthesia used 22 times was not followed by spread Endotracheal tubes were used in 494 general anesthetics with a 10 9 per cent incidence of spread In 289 general anesthetics no tube was used and incidence of spread was 9 3 per cent Although 36 different combinations of anesthetic agents and technics were employed none seemed particularly responsible for spread

[Since the type of anesthesia may not be of major importance it becomes obvious that other safeguards against progressive disease should be used These include the timing of an operation to take place preferably late in the morning after the patient has expectorated most of his accumulated discharges and careful postoperative supervision to avoid long period of unconsciousness and aspiration of secretion or exudate —Ed]

Venous Thrombosis and Pulmonary Embolism in Tuberculosis Daniel W Zahn and Charlotte T Peirce (Fort Logan Colo) found in 1 700 autopsies on tuberculous subjects that pulmonary embolism and/or peripheral venous thrombosis had occurred in 36 (2 1 per cent) an incidence less than one third that in autopsies on nontuberculous patients at Fitzsimons General Hospital In six cases thromboembolic features developed within 21 days of operation and death was due to postoperative embolism In four instances the clinical picture of congestive heart failure was confirmed at autopsy Since the study was concerned only with thromboembolism and its relation to use of bed rest in tuberculosis these cases were withdrawn from the series and the incidence corrected to 1 5 per cent Further analysis revealed that among the 26 cases thromboembolism occurred as a terminal manifestation in 22 and was unrelated to the cause of death In three cases the cause of death was a pulmonary embolic accident In the remaining case massive tuberculous mediastinal nodes compressed the lumen of the superior vena cava producing thrombosis

Postoperative and cardiac patients excluded the group s average age was 33 5 Average age of 148 non

( ) Am J M d S 167 8 N 1 1949

tuberculous patients with pulmonary embolism or peripheral venous thrombosis was 51 1 years

The difficulty with which the source of embolism is demonstrated and the large number of cardiac patients which make up this series suggests that cardiac mural thrombi may be a more important source of emboli than peripheral venous channels When venous thrombosis is detected it is usually in the lower extremities where it was found at autopsy in 76 per cent of tuberculous subjects with thrombosis and in 70 8 per cent of nontuberculous subjects Source of emboli in a significant number of cases was pelvic and abdominal veins Periprostatic veins left spermatic vein and corpora cavernosa of the penis were obscure sources of pulmonary emboli There was no correlation between duration of bed rest for tuberculous patients and incidence of thromboembolism

No satisfactory reason has been found to explain the low incidence of thromboembolism in tuberculosis Low prothrombin time high fluid intake frequent cough and indulgence in the Mueller experiment (forced inspiration with a closed glottis) may individually contribute to the low incidence but the extent of these contributions is pure conjecture Although age is the only objective difference between tuberculous and nontuberculous groups civilian experience does not indicate that this is a significant factor

Thromboembolism does not constitute a significant threat to tuberculous patients being treated with strict bed rest

[This study bears out the general experience that pulmonary embolism is seldom observed in tuberculosis hospitals where many patients rest in bed for many months There seems to be a great difference in this respect between tuberculous patients who as a rule move about in bed and those patients particularly the elderly who lie completely immobilized In this connection it is interesting to note the experience of Blodgett (Bull New York Acad Med 25 176-184 March 1949) at Peter Bent Brigham Hospital Statistical analysis of surgical cases did not disclose that early rising reduces the incidence of atelectasis or phlebitis although he did show that early rising has no apparent ill effect on wound healing —Ed]

***Survey of Valvular Heart Disease in 1,000* Cases of Pulmonary Tuberculosis** Harold L Neuenschwander Jerry R Miller and John F Briggs[3] (Ancker Hosp St Paul) found some degree of heart involvement in 17 7 per cent of the cases reviewed The mitral valve was involved in 11 1 per cent and frank advanced mitral stenosis occurred in 0 5 per cent The aortic valve was involved in 9 7 per cent and the tricuspid valve in 0 7 per cent The pulmonary valve showed a slight change in about 0 5 per cent Most aortic valve defects occurred in men and mitral lesions predominated in women

Tuberculosis was the chief cause of death in 49 3 per cent and heart disease in 8 2 per cent The rest died of various other illnesses

It is interesting that no true pulmonary stenosis occurred in this group this casts suspicion on the popular belief that persons with pulmonary stenosis are more susceptible to tuberculosis than others The old dictum that pulmonary congestion incidental to heart disease protects against tuberculosis is fallacious because the incidence of mitral stenosis in tuberculous patients is about the same as in the nontuberculous group in this area

[This study helps to clear up some erroneous clinical impressions The theory that circulatory differences in the apex and base of the pulmonary lobe have a direct relation to the localization of progressive tuberculosis must still be regarded as unproved until further evidence is at hand —Ed]

NEOPLASMS AND CYSTS

Cancer of Respiratory System in United States Chromate-Producing Industry Willard Machle and Frederick Gregorius[4] analyzed mortality data of the chromate producing industry (six plants) Death rate for cancer of the respiratory system was high among exposed employees Of 193 deaths from all causes 66 were due to

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(3) Minnesota Med 3 378 379 Apr 1 1949
(4) Pub Health Rep 63 1114 11 7 Aug 27 1948

cancer 42 being from respiratory system cancers This is 16 times the expected ratio of 1 4 per cent Crude death rate for lung cancer was 25 times the normal range of excess for various plants being from 18 to 50 fold

For the group aged 50 and under over all cancer rate ranged from 2 to 11 times normal and for persons over 50 from 1½ to 8 times normal Rates for cancer of the respiratory system were high for both age groups but the rate for the younger group was 20 70 times that for the control population whereas for the older group it was 10 40 times that for the control population

In one plant in which there was significant exposure only to bichromates and chromic acid no respiratory system cancer occurred whereas in a comparable plant in which exposure was to all compounds of chromium respiratory cancer rate was 18 times the normal This suggests that exposure to certain compounds of chromium is not necessarily associated with high rates of lung cancer and that the carcinogenic chromium compounds are the monochromates Since nasal irritation and septal irritation occurred in both plants these signs do not necessarily imply exposure to kinds and quantities of chromium compounds capable of producing lung cancer

Data on severity method and duration of exposure were insufficient for statistical use Mean duration of exposure before onset was 14 5 years Contributory factors such as age sex race constitutional type heredity and occurrence of other disease could not be properly assessed Data obtainable were insufficient to permit conclusions or comment on symptoms signs therapy pathology and clinical course

[Industrial hazards of this nature are difficult to evaluate Most of the statistical evidence suggests that ordinary dust and fumes as of silica do not increase the incidence of lung cancer however Lynch and Cannon (Dis of Chest 14 874 889 Nov Dec 1948) believe that it is still an open question whether there is a higher incidence among asbestos workers Suspicion is also directed against tar and arsenic (Editorial J A M A 140 408 410 May 28 1949) Obviously further study is needed —Ed]

Cytology of Bronchial Secretions Its Role in Diagnosis of Cancer William L Watson Henry Cromwell Lloyd Craver and George N Papanicolaou[5] (Memorial Hosp New York City) studied the cytology of sputum bronchial aspirations or both in 400 patients of whom 236 were proved to have bronchogenic cancer Bronchial aspirations were positive in 27 and sputum positive in 112 giving an accuracy rate of 60 per cent In recent cases accuracy rate has risen to nearly 90 per cent

METHOD—For sputum examination material is collected after coughing and fixed immediately in 70 per cent alcohol Routinely three 24 hour specimens are studied Smears are made and fixed in alcohol ether and stained first in hematoxylin and then in OG6 and EA65 Bronchial aspirates are obtained by introducing a suitable cannula through the bronchoscope into the suspected branch bronchus The patient is turned until the suspected portion of lung is dependent the syringe containing 2 5 cc normal saline is attached to the cannula and the fluid is slowly injected The patient is then shaken gently and after three minutes the collection bottle is attached to the cannula suction applied and the patient turned back to elevate the suspected portion of lung above cannula tip Collected material is placed in a bottle containing 70 per cent alcohol

Figures 35 and 36 illustrate findings in a bronchial aspirate and a histologic section of tumor from the same patient This method is simple inexpensive and reliable in the hands of experienced cytologists permits early recognition of incipient or hidden carcinoma is useful as a screening method on a large scale complements well established methods of pathologic diagnosis and may be of value in following results of operative procedures and x ray or mustard gas therapy Location of the cancer grade of malignancy and type are not always clear Cytologic studies tend to lessen intervals between initial clinic visits and hospitalization for surgical care because they aid in selecting suitable cases and cutting down the number of hospital days before surgery If the thoracic surgeon is to cure more patients with bronchogenic cancer he must see them earlier Internists should view with suspicion atypical pneumonia in a patient over 35 and

(5) J Th c S g 18 113 1 F b y 1949





Fig 3 (t p) —B h l w h g p l w g l \ ll
Fig 36 (b t m) —S m H t l g t f p t t m n h w g p d m d m g d ll
(C t y f W t on W L t l J Th S g 18 113 1 F b y 1949)

every patient with recurring virus pneumonia or un resolved pneumonia should have bronchoscopy and complete cytologic studies

[In ca s of lu g cancer cytologic studie have attracted wid attentio and in well organ ed cl ic and laborat r es ar prov

ing to be highly reliable Proper technic and experienced pathologic interpretation are extremely important When apparent discrepancies are found in cytologic and clinical observations further efforts at confirmation should be made particularly to avoid a mistaken diagnosis of cancer which may lead to complete removal of a lung The diagnostic problem is most important in the case of peripheral lesions inaccessible to bronchoscopic view Much reliance should be placed on a careful history of the illness as well as on other findings —Ed]

Primary Carcinoma of Lung Diagnosis by Cytologic Studies of Sputum and Bronchial Secretions Seymour *M Farber Mortimer A Benioff and Gerd Tobias*[6] *(San Francisco)* state that malignant cells can be demonstrated in sputum or bronchial secretions in at least 80 per cent of all patients with primary carcinoma of the lung Sputum or bronchial secretions can be prepared anywhere and submitted to experienced observers

METHOD—Selected material from sputum or bronchial secretions may be smeared on slides and fixed while still wet in equal parts of ether and 95 per cent alcohol After two hours fixation slides may be stained immediately by the Papanicolaou technic or dried and mailed to laboratories where trained personnel can examine them If the slides cannot be prepared immediately after collection of sputum or bronchial secretion the material may be fixed in jars containing 10 cc fixative solution and slides prepared later

The authors studied 1 512 specimens prepared in this manner from 414 patients suspected of having carcinoma of the lung Positive or suspicious cells were found in 69 cases Carcinoma of the lung was confirmed pathologically in 56 cases Cytologic examination revealed or suggested carcinoma in 46 of these patients Sputum smears were obtained in 52 cases of proved malignant disease In 43 of these cells were found which indicated or suggested carcinoma of the lung

Cytohistologic Study of Bronchial Secretions Howard L Richardson Warren C Hunter William S Conklin and *Arthur B Petersen*[7] *(Univ of Oregon)* report a study of bronchial aspirations from 167 patients

All material collected at bronchoscopy was fixed in formalin* and placed in aqueous picric acid solution

(6) C l f a M d 60 95 99 A gu t 1948
(7) A J Cl Path 19 3 3 3 7 Ap il 1949

Solid material was imbedded in paraffin and sections were cut and stained with hematoxylin eosin and orange G Two sections were examined from each block

Forty eight patients were submitted to standardized studies under the direction of one bronchoscopist Pulmonary neoplasm was diagnosed in 36 instances in 35 of which the diagnosis was verified in a bronchial biopsy specimen obtained at operation or autopsy biopsy was not done in 1 In no case was biopsy positive and cytohistologic study negative In 119 cases studied by non standardized procedures biopsy revealed carcinoma not diagnosed by histocytologic study in 4 Carcinoma of the lung did not produce any pathognomonic exudate

Immediate fixation of bronchial aspirations utilization of all material obtained standardization of technic and services of an experienced bronchoscopist are essential for accurate diagnosis of cancer of the lung by this method The cytohistologic method is as satisfactory as if not superior to the smear technic

[This technic seems to offer certain advantages depending on the experience and preference of the cytologist No doubt others will wish to explore the comparative merits of this and the smear technic —Ed]

Tumor Cells in Bronchial Secretions Experimental and Statistical Study Max Appel (Champaign Ill) and Theodore T Bronk[8] (Chicago) transplanted Brown Pearce rabbit testis tumor into the bronchi of rabbits to determine how soon after tumor growth is established tumor cells can be identified in bronchial secretions Smears were taken every third day beginning the sixth day after transplantation The sixth day 58 per cent of the animals had positive smears and all showed positive smears by the end of the third week

In none of the 17 animals showing tumor cells at six days could tumor be recognized grossly or by x ray but tumor nodules could be seen microscopically in autopsy material The earliest time at which tumor could be recognized grossly was 10 or 20 days after transplantation

(8) Am J Cl P th 19 3 0 3 Ap 1 1949

Obstructive Pneumonitis of Neoplastic Origin Interpretation of One Form of So Called Atelectasis and Its Correlation According to Presence or Absence of Sputum John R McDonald Stuart W Harrington and O Theron Clagett[9] (Mayo Clinic) have found the most frequent cause of sputum to be a secondary lesion incorrectly called atelectasis in the periphery of a lung which drains into an obstructed bronchus The term obstructive



Fig 37 —Small at ll type f t h g r m f pper lobe —l b Tl r ked b l tr ti p mo t w th nt a t re Th ke g ot ac l pl r ly g p m l c p x es i t (C t y f M D all J R et l J Th a S rg 18 97 11 F br y 1949)

pneumonitis is preferred to designate the peripheral pulmonary changes

In early stages the obstructive bronchial lesion dams back secretion into the bronchi and alveoli The involved portion of lung is usually reddish and more voluminous than normal In this and subsequent stages the involved lobe or lung is airless Inflammatory cells bacteria mucus and serum are found in the affected tissue As the

(9) J Tho c Su g 18 9 11 F b a y 1949

lesion progresses lipoid filled phagocytes are seen in the pneumonic area Organization of the exudate ensues with collagen and fibrous tissue formation which be comes more marked as time goes on Endarteritis affect ing both arteries and veins may progress to complete occlusion and is an expression of lack of function of the lobe with diminished need for blood This condition leads to contracture of the lobe (Fig 37) and at this stage it is firm brownish or gray with thickenin of the over lying visceral pleura Less commonly there is abscess formation and the usual complications of abscess may follow Since the neoplasm causing bronchial obstruction is not static some bronchi have been obstructed more recently than others and there is considerable variation in the process Mucopurulent fluid accompanying pneu monitis forms most of the sputum in most patients with bronchial neoplasms Ob tructive pneumonitis in the presence of an adequate bronchial airway may result in physiologic block to egress of secretions brought about by replacement of ciliated columnar cells by carcinoma cells or splinting of the bronchial wall due to neoplasm infiltration Often when obstruction is removed the pneumonitis clears up

There is a high degree of correlation between amount of obstructive pneumonitis and amount of sputum Spu tum in patients with adenomas and in those with bron chogenic carcinoma is evidence that replacement of nor mal mucosa with carcinoma is seldom a factor by itself in sputum production Sputum was present in *26* of *37* patients who had adenomas and in 1 of *2* who had al veolar cell carcinoma Of 118 patients who had broncho genic carcinoma 37 gave no history of sputum The more peripheral the situation of carcinoma the less the chance for sputum because obstruction of a larger bronchus and production of obstructive pneumonitis is less likely Be cause of the more frequent peripheral location of the lesions this was particularly true of adenocarcinoma and large cell indeterminate types of bronchogenic cancer Of 14 [illegible] with metastatic neoplasms 8 had sputum

In several cases in which absolute correlation between quantity of sputum and severity of obstructive pneumonitis was lacking central necrosis of the tumor with evacuation through the bronchus accounted for the discrepancy There was no correlation between presence absence or amount of sputum and duration of symptoms and location of lesion

[Most bronchial carcinomas originate in the main stem or lobar bronchi and frequently it is the obstructive pneumonia that first brings the patient to the physician Unless the potentialities of such pneumonias which parade under the terms atypical pneumonia unresolved pneumonia and organizing pneumonia are appreciated the diagnosis may easily be missed As a rule careful history and physical and x ray study will lead without difficulty to the identification of this type of pneumonia This article should be studied in connection with the following one by Brock —Ed]

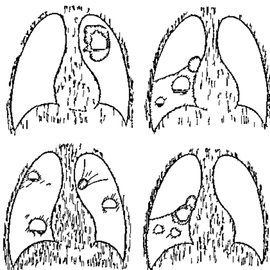
Studies in Lung Abscess Lung Abscess and Bronchial Carcinoma Of 405 lung abscesses R C Brock[1] found bronchial carcinoma the cause in 56 (13 8 per cent) Since 53 patients were over 45 incidence of malignant growth as the primary cause of abscess in persons past 45 was 30 per cent and thus far greater than the incidence for all other ages Only three patients were women

In primary malignant lung abscess (35 cases) the growth is commonly circumscribed or parenchymatous and usually forms a round oval or slightly lobulated mass in the substance of the lobe Abscess is due to breaking down of the growth itself (Fig 58) and almost invariably the cancer is of squamous cell type Size and character of the abscess vary considerably and the lesion may contain one or several small cavities in the middle of a massive opacity (25 cases) The cavity may be large with thin or moderately thick wall which presents nodules Between these extremes the abscess may be of moderate size and placed eccentrically in the opaque area Erosion of overlying ribs is virtually diagnostic of cancer Accurate differentiation of a primary from a secondary abscess due to growth may be difficult since an infected breaking down growth may also give rise to an infected lobe containing an abscess resulting from in-

(1) G y Ho p Rep 9 3 36 1948

fection but in direct continuity with the primary growth (Fig 41)

When a lobe or lung is infected behind an obstructing *primary bronchial growth (Fig 39) the most common* process is diffuse septic pneumonitis with gross septic



Fg 38 (p l ft) —P m y b d t b k g l w g owth
Fg 39 (top ght) —S d y t oc g l t cted f t d l be d t l t m Oft n m th b p t
Fg 40 (b ttom l ft) —S d y b ou t l by f ll f on f om p m y ci om n l ft pp l be
Fg 41 (b tt m ght) —Ab s l so t w th b ak g d w g wth wh h lso g l t t d f t on f l b wh h se d y b d l p
(C t y f B k R C G y H p R p 97 75 86 1948)

bronchiectasis The 17 secondary lung abscesses of this type were commonest when obstruction was incomplete or intermittent These abscesses may be small several cavities may form or a large solitary abscess may be present When bronchial obstruction becomes complete the solid part of the infected organ dominates the clinical and x ray picture This type abscess may be caused by any growth (benign or malignant) that obstructs a

bronchus In some cases the abscess cavity is formed by gross dilatation of a single bronchus

There were four cases of secondary lung abscess due to spill over infection from a primary growth elsewhere in the lungs (Fig 40) The lesions were usually small and localized but may be diffuse and spread to affect a whole lobe When the process occurs in the opposite lung it usually involves one of the classic sites for an inhalation lesion Diagnosis in this type case may be confusing and the possible course of events should be remembered when one is confronted with multifocal or bilateral lung suppuration in patients over middle age The primary growth may be of any type that causes infection and is more commonly one affecting a lobar or segmental bronchus

Lung abscess due to carcinoma may manifest itself as a febrile illness with purulent sputum and other signs of infection or infective features may be slight or absent and diagnosis made chiefly by x ray demonstration of a lung cavity usually with a fluid level and surrounded by an opaque zone In this series the left upper lobe was affected nearly twice as often as others and no abscess occurred in the middle lobe Cough may be an early symptom and blood staining of sputum a significant feature In febrile cases associated with copious purulent sputum simple lung abscess is usually diagnosed and often the presence of carcinoma is difficult to establish The pleura may be involved with effusion progressing to empyema in some cases In secondary malignant lung abscess the x ray features are not as distinctive but glandular and visceral metastases are much more common than in primary forms Bronchoscopy is of great value in diagnosis

Some form of operation was performed on 17 patients Pneumonectomy done on six is the procedure of choice Palliative external drainage may be performed in elderly frail poor risk subjects when cough and persistent production of abundant sputum are so burdensome that relief is mandatory

Cytologic Changes in Bronchogenic Carcinoma Following Treatment with Nitrogen Mustard (Methyl Bis [β Chloroethyl] Amine) Edward A Gaensler Donald G McKay Paul F Ware and Joseph P Lynch[2] (Boston City Hosp) studied biopsy specimens of bronchogenic carcinoma obtained before during and after nitrogen mustard treatment in 12 patients In four cases post treatment specimens showed no tumor tissue histologically in an area previously known to contain tumor

Findings in all other post treatment specimens were similar to those frequently observed in tumors not subjected to toxic substances or irradiation Formation of large giant cells with enormous multilobar nuclei nuclear fragmentation disintegration of cells and cell groups focal necrosis and variations in granularity and staining reactions were seen frequently In comparison with pretreatment specimens all had definite changes in histologic appearance The most unquestionable and striking changes occurred in the most differentiated types Increase in number of mitoses giant cell formation and nuclear and cellular disintegration were most prominent in this group Least pronounced changes occurred with undifferentiated cell types and included necrosis not observed in the pretreatment specimen and decrease of mitotic activity Gross reduction in size of tumor as well as favorable clinical response were most noticeable in the undifferentiated types Changes following nitrogen mustard treatment are practically identical with those seen after ionizing irradiation

Clinical results could be correlated with morphologic observations Among 60 patients treated 54 per cent showed objective improvement Favorable results occurred in 83 per cent of undifferentiated tumors 50 per cent of squamous cell tumors 33 per cent of adenocarcinomas and 11 per cent of epidermoid carcinomas

Autopsy material was available for study in eight cases Three patients died of toxic effects of large doses of nitrogen mustard and the rest of miscellaneous

( ) A h Path 46 533 518 D mbe 1948

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The six patients from a tuberculosis hospital had a diagnosis of far advanced pulmonary tuberculosis and all had positive sputum Four of the five carcinoma patients from the general hospital had a diagnosis of carcinoma and had sputum negative for tuberculosis

In the general hospital patients bronchial tumor was the more prominent disease and seems to have been followed by active pulmonary tuberculosis This course was favored by the generalized debilitating effect of carcinoma and the local pulmonary destruction caused by it In the patients from the tuberculosis hospital active infection seemed to precede bronchogenic carcinoma and the occurrence of the two diseases was purely coincidental Their coexistence is due simply to the fact that persons with pulmonary tuberculosis now belong to an older age group Presence of carcinoma is not antagonistic to progress of tuberculosis

Irradiation was given four patients after carcinoma was diagnosed In two of these tuberculosis was definitely activated by irradiation in one it was possibly activated and in one no effect was apparent

In 6 of the 11 cases of cancer a diagnosis might have been made had a second major disease been suspected but in the other five the coexistent disease gave no sign

[A discussion of the significance of this combination has also been presented by Drymalski and Sweany (Am Rev Tuberc 58 203 206 August 1948) —Ed]

Pulmonary Adenomatosis Report of Three Cases is presented by George W Drymalski J Robert Thompson and Henry C Sweany[4] (Mun Tuberculosis Sanatorium Chicago) Pulmonary adenomatosis results in multiple nodular tumors of the lungs Evidence indicates that it is a hyperplastic process of the lining cells of the alveoli or terminal bronchioles caused by nonspecific irritants This response eventually causes death by extensive involvement of lung parenchyma or by progressing to true malignancy

Gross pathology of pulmonary adenomatosis usually

(4) Am J P th 24 1083 1093 S pt mb 1948

causes No patient receiving 0 4 mg/kg body weight showed toxic manifestations beyond brief leukopenia All who died of toxic manifestations received 1 5 mg/kg or more

Lower doses of nitrogen mustard only caused diminution of myelopoietic tissue in bone marrow with deposition of hemosiderin there and in the spleen Toxic doses caused compression of lymph node reticulum and connective tissue and disappearance of all lymphocytes which were replaced by numerous plasmacytes and macrophages Numerous clumps of plasmacytes hemosiderin deposition and complete disappearance of malpighian corpuscles were observed in the spleen following toxic doses The only cells in the marrow of these patients were small collections of plasmacytes and a few macrophage type cells

Two deaths were due to overwhelming sepsis both patients having received full doses of penicillin for two weeks before death suggesting that nitrogen mustard may inhibit the antibody mechanism

[Clinical experiences with nitrogen mustard have been no more encouraging than those with radiotherapy Some workers are now *trying a combination of the two* Surgical resection if feasible remains the most promising method of *treatment*—Ed]

Coexistent Bronchogenic Carcinoma and Active Pulmonary Tuberculosis Edward Robbins and Gertrude Silverman[3] (New York City) present histories of 11 patients with bronchogenic carcinoma and 1 with bronchial adenoma all with coexistent active pulmonary tuberculosis *All* patients with cancer were men Average age was 52 The patient with adenoma was a *woman 42* All had a productive cough of 4 months to 14 years duration but only one had blood tinged sputum and none had gross hemoptysis Chest pain occurred in eight in six on the side of the carcinoma Seven had sputum positive for tuberculosis In none of five patients examined bronchoscopically was endobronchial tumor or obstruction diagnosed but two showed evidence of endobronchial tuberculosis or tuberculous granulation tissue

(3) Cancer 2 65 97 Jan ary 1949

slight thickening Absence of invasion is characteristic Alveolar spaces contain desquamated cells occasional phagocytes exudate and mucus Significant features of the condition are often obscured by bronchopneumonia

In reported cases average age was almost 54 Duration of the disease varied from several weeks to over two years Inaugural symptoms are usually dyspnea and a cough productive of mucus Radiologically the condition simulates tuberculosis carcinoma or pneumonia

CASE 1—Woman 34 was hospitalized because of two attacks of bronchopneumonia A routine x ray 18 month previously had shown a 3 cm cavity in the right lower lobe but no tubercle bacilli were found in the sputum and bronchoscopy was negative On admission an x ray showed consolidation and atelectasis of the right lower lobe Diagnosis was chronic lung abscess of undetermined origin complicated by pneumonitis and bronchiectasis and lobectomy was performed The right lower lobe was firm throughout Its cut surface was uniformly solid and resembled the gray hepatized stage of pneumonia (Fig 42) The microscopic picture was characteristic (Fig 43)

CASE 2—Woman 55 was seen because of cough with occasional blood streaked sputum of six month duration Chest expansion was limited and resonance was impaired in the upper third of the right lung and entire left hemithorax X ray revealed areas of haziness in both lungs Sputum examination revealed no tubercle bacilli but many epithelial cells with vesicular nuclei and eosinophilic cytoplasm Some nuclei were hyperchromatic Diagnosis of pulmonary carcinoma was made and confirmed by aspiration biopsy of the lung and finally by autopsy On section both lungs contained several firm dull gray areas similar to gray pneumonic hepatization Histologic picture was typical

CASE 3—Woman 45 with proved pulmonary tuberculosis was hospitalized because of 35 lb weight loss and progressive pulmonary disease X rays showed infiltration of both lungs Neither malignant cell nor tubercle bacilli could be found in sputum At autopsy the entire right lung was consolidated and on section was gray and hepatized In the left lung a similar lesion fanned out from the hilus to the pleura laterally and to the base posteriorly Microscopic study revealed abnormalities typical of pulmonary adenomatosis

Lobar Adenocarcinoma of Lung Simulating Pneumonia Report of Two Cases is presented by Gertrude

resembles gray pneumonic hepatization Microscopically the picture is characterized by nonciliated cuboidal or columnar cells lining otherwise unaffected alveolar walls





Fig 42 (top) —Right low lobe h w g r gg d I rat n d g ay c sol dat on

Fig 43 (bott m) —S me c se as p eced g Abrupt t sf rmat of br chiola p th l m t nonc iated c l mna lls and ad om to ll l n g u ffected al eol r wall × 300

(Courtesy of Drymalsk G W t l Am J Path, 24 1083 1093 S ptem ber 1948)

The cytoplasm of these cells is eosinophilic granular or somewhat foamy Goblet formation and a brush border may be noted Cells are uniform and mitotic figures un common Alveolar septa are not involved or show only

slight thickening Absence of invasion i characteristic Alveolar spaces contain desquamated cells occasional phagocytes exudate and mucus Significant features of the condition are often obscured by bronchopneumonia

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CASE 3—Woman 45 with proved pulmonary tuberculosis was hospitalized because of 25 lb weight loss and progressive pulmonary disease X ray showed infiltration of both lungs Neither malignant cells nor tubercle bacilli could be found in sputum At autopsy the entire right lung was consolidated and on section was gray and hepatized In the left lung a similar lesion fanned out from the hilus to the pleura laterally and to the base posteriorly Micro copic study revealed abnormalities typical of pulmonary adenomatosis

Lobar Adenocarcinoma of Lung Simulating Pneu ~~t of Two Cases is presented by Gertrude

Silverman and Alfred Angrist[5] (Queens Gen l Hosp Jamaica N Y)

CASE 1 —Woman 31 was hospitalized because of an illness of six months characterized by cough and pleuritic pain in the right chest X ray showed nodular fibrosis of the entire right



Fg 44 —F lm t k 48 h b f d th h w g d ffu h m g n o s h d w th gh ut ght d of th x a d nod l filt t l ft l g (Cou t y f S l m n G a d A gr t A A h I t M d 81 369 380 M h 1948)

chest with thickened pleura and increased pulmonic markings in the left lung A month later similar nodular infiltration de veloped on the left side Sputum contained no acid fast bacilli The disease progressed and just before death x ray (Fig 44) revealed dense homogeneous shadows throughout the entire right thorax and nodular parenchymal infiltration in the left lung

(5) Ar h I t M d 81 369 380 M r h 1948

Autopsy revealed a completely solidified right lung (Fig 45) and nodular infiltration in the left lung Microscopic examination showed diffuse adenocarcinoma infiltrating the alveolar walls Alveoli were lined by columnar tumor cells Tumor cells were also found in lymphatic vessels hilar lymph nodes adrenals and kidney Pathologic diagnosis was diffuse adenocarcinoma of the right lung with local and distant metastases

CASE 2—Woman 73 was hospitalized because of cough and blood tinged sputum of two months duration X ray



Fig 45—Complet ly l d f d ght l g w th nod la nfilt t n th gh t l ft l g (C rt y f S l rm G d A g A A h I t M d 81 369 38) M h 1948)

showed increased density in the lower half of the right lung and another area of increased density in the upper lobe Hilar shadows were prominent bilaterally Though tuberculosis was suspected tubercle bacilli were not found in sputum at any time during the subsequent five months

Autopsy revealed the right lung to be completely consolidated and the cut surface firm gray and so mucoid that a diagnosis of lobar pneumonia was made Microscopic examination revealed alveoli lined by mucus secreting tumor cells In addition the cells were tall columnar and nonciliated They lined the alveoli in single or in several layers and the lining was frequently thrown into papillary fold projecting into the acinar lumen In the left lung tumor extension along peribronchial and

Silverman and Alfred Angrist (Queens Gen'l Hosp Jamaica N Y)

Case 1 W man of ... was hospitalized because of an illness ... ch ... cough and pleuritic pain in the right ... X-ray showed nodular fibrosis of the entire right



Fig 44 — ...

... Med 81 369 333 ...

chest with thickened ... in the left lung. A month later ... in the left ... Sputum ... nodular ... The ... progre... ... but later death ... tubercle bacilli ... right thorax and nodular ... throughout the entire lung ... infiltration in the left (Fig 44)

... M ...

... 1 48

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perivascular lymphatic vessels was noted Metastases were found in adrenals and liver Pathologic diagnosis was diffuse mucogenic adenocarcinoma of the lung with local and distant metastases

Review of 4 500 consecutive autopsies revealed lung consolidation in 3 of 79 patients with metastatic adenocarcinoma to the lung and in 2 of 26 patients with primary adenocarcinoma of the lung Since primary foci of carcinoma outside the lung may be minute in such cases they should be looked for carefully Absolute proof of origin of malignancy in alveolar wall has not been thoroughly established Nor has multicentric origin been established and there is no proved relation between diffuse adenocarcinoma of the lung and pulmonary adenomatosis

[This condition is seldom diagnosed during life but cytologic study of the sputum will probably reveal the true condition in some cases —Ed]

Bronchial Adenoma Carlton R Souders and J W Kingsley Jr [6] (Lahey Clinic) studied 15 bronchial adenomas representing 6 9 per cent of all lung tumors seen since 1930 With few exceptions bronchial adenomas are situated in a primary bronchus where they are visualized easily with the bronchoscope In 12 of the 15 cases the tumor was visualized bronchoscopically Typically the rounded pink or red purple mass has a bosselated surface and usually a broad base though occasionally these tumors were pedunculated Frequently blood vessels were seen on the surface Profuse bleeding from bronchial adenomas is notorious

Carcinoma often produces fixation of the bronchus but this almost never occurs with an adenoma Carcinomas are frequently ulcerated Biopsy has value but has certain shortcomings Forceps may not penetrate the tumor deeply enough to obtain characteristic cells and squamous metaplasia or cell distortion may simulate malignancy

Nine patients were under 40 and therefore not in the

(6) New England J Med 239 459 466 Sept 3 1

cancer age Duration of symptoms varied from 8 months to 6 years (average 2½ years) Cough was the commonest symptom and was most troublesome at night when the patient assumed a particular position Hemoptysis was common and usually of sudden onset and termination In most cases bleeding resulted from rupture of a surface blood vessel Wheeze occurred in three patients and dyspnea in four Chest discomfort was described as a feeling of fulness or pressure Four patients had recurrent pneumonia two repeated chills and fever and two pleurisy

Physical findings were characteristic of partial bronchial obstruction but in six patients chest examination was negative Chest x rays revealed abnormalities in most cases but special technics were frequently necessary and final diagnosis rested on bronchoscopic and pathologic study Atelectasis alone was demonstrated in three cases a mass in three inflammatory infiltration or bronchiectasis in two and various combinations of these findings in four Fluoroscopy and x rays taken during forced expiration revealed obstructive emphysema in some patients Bronchography was used when bronchoscopy failed to determine the tumor site and when bronchiectasis was present

Bronchial adenoma should be considered in young patients with chronic cough hemoptysis and repeated chest infections Atelectasis localized wheeze obstructive emphysema or unilateral bronchiectasis constitute further suggestive evidence

Therapy is limited to local removal and surgical resection Bronchoscopic removal is feasible when there is a distinct pedicle and no extrabronchial extension with irreversible pulmonary damage and is the only possible approach to tumors involving the carina It may be used to promote bronchial drainage before resection Surgical resection permits removal of bronchiectatic areas and precludes possibility of subsequent malignant degeneration

Roentgenologic Significance of Hamartoma of Lu g In a report of four cases Wendell C Hall[7] (Hartford, Conn) states that lung hamartomas arise in abetrant anlagen and contain some or all of the normal his ologic elements which mal e up mature bronchi or lung tissue although these are quantitatively grouped in abnormal proportions so that one element usually cartilage pre dominates Most so called chondromas of the lung are



F g 46—Ham t m f left l (C u t y f H ll W C Am J Roent g n l 60 605 611 No mber 1948)

actually hamartomas Usually they are firm smooth or lobulated and have the appearance or consistency of cartilage Although their size varies from less than 1 mm to huge masses which fill one side of the chest most are under 1 cm They are beni n and self limiting except in rare instances in which malignant transformation oc curs

Most lung hamartomas are asymptomatic and are dis

(7) Am J Roentge l 60 605 611 No emb 1

covered incidentally The cartilaginous masses almost always show calcification or ossification and may appear on x ray as shown in Figure 46

[There is a tendency to remove surgically all questionable lung tumors However this is not usually necessary when hamartomas can be identified as such and are not so situated as to cause obstructive pneumonia —Ed]

Study of Intrathoracic Cysts Arising from Diaphragm P E A Nylander and S J Viikari[8] (Helsinki) present

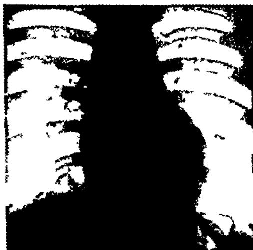


Fig 47—P [illegible] film [illegible] cyst [illegible] (C [illegible] Nylander P E A [illegible] Viikari S J Ann chir et gyn Fenn 37 99 114 1948)

three cases Although the cysts were slightly adherent to the pericardium in two they were broadly attached to the diaphragm (Fig 47) and received their blood supply from it All were located in the ventral median part of the right half of the diaphragm a point corresponding roughly to the infracardiac bursa

According to Broman this bursa is a remnant of the right pneumatoenteric recess developed from the original

(8) A [illegible] F [illegible] 37 99 114 1948

Roentgenologic Significance of Hamartoma of Lung In a report of four cases Wendell C Hall[7] (Hartford Conn) states that lung hamartomas arise in aberrant anlagen and contain some or all of the normal histologic elements which make up mature bronchi or lung tissue although these are quantitatively grouped in abnormal proportions so that one element usually cartilage predominates Most so called chondromas of the lung are



Fig 46—Hamartoma of left lung (Courtesy of Hall W C Am J Roentgenol 60 605 611 November 1948)

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(7) Am J Roentgenol 60 605 611 Nov 1948

Influenza virus was isolated from 13 of 36 patients with bacterial pneumonia occurring during the influenza epidemic in March and April 1947 The 13 patients all had pneumococcic pneumonia two having bronchopneumonia and the others lobar pneumonia Type I pneumococcus was the etiologic agent in six cases and type XXX in two other types caused one case each There was no correlation between day of disease and ability to isolate virus from sputum Viru was isolated from six specimens on or after the fifth day probably because it descended with the pathogenic bacterium to the lower respiratory tract and persisted and multiplied in respiratory epithelium of the bronchial tree longer than i ordinarily persists in epithelial cells of the upper respiratory tract Serologic tests were positive for 8 of the 13 patient and for 4 from whom no virus was isolated Thus 47 per cent of patients with pneumonia during an influenza epidemic gave positive evidence of dual infection The 13 virus strains were similar to each other to the reference 1947 strain of influenza A and to strains of influenza virus isolated from patients with uncomplicated influenza during the same period

Lungs from two patients who died of primary pneumonia and two with fatal secondary pneumonia yielded influenza virus as the only pathogen All cases occurred during an interepidemic period three were caused by influenza A strains and one by influen a B Histologic examination of the lungs in two cases failed to show evidence of consolidation bronchitis or interstitial pneumonia

From these results it seems that often during influenza epidemics and occasionally durin nonepidemic periods bacterial pneumonia is in some way related to recent or concurrent infection with influenza virus Pathogenesis of these multiple infections is not understood but it eems unlikely that influenza virus alone is often responsible for severe pneumonia The most generally accepted relationship between these two agents is that virus decreases general host resistance and predi poses to bac

pleuroperitoneal coelomic cavity It appears early and when the rudiments of dorsal diaphragm are fused medially the walls of the right pneumatoenteric recess become tightly pressed together and grow into one By this process the cranial part of the original recess becomes isolated and remains as an infracardiac bursa between the esophagus right lung and right half of diaphragm Although there are bursas on both sides of the esophagus the left one usually atrophies In adults the right normally occurs as a small slit between esophagus and right half of diaphragm In several mammals it constitutes the third pleural cavity and grows to a much larger size than in man Therefore it seems possible that in man the bursa may be larger than normal and survive as a persistent congenital cyst In the authors cases the endothelial layer was similar to that lining the original coelomic cavity and coelomic cysts of the pericardium

Although the difficulties in differential diagnosis between these cysts and other intrathoracic neoplasms is considerable early diagnosis is important so that proper treatment of malignancy will not be delayed Operation is the indicated treatment if there is no definite contraindication Surgical removal of the cysts presented no difficulties in the authors three cases

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PNEUMONIA

Relation of Influenza Virus and Bacteria in Etiology of Pneumonia Of 33 sputum specimens obtained from patients with bacterial pneumonia between influenza epidemics Elizabeth Starbuck Maxwell Thomas G Ward and Thomas E Van Metre Jr [9] (Johns Hopkins Univ) isolated influenza virus from only 1 and serologic tests for influenza were negative for all patients The positive sputum specimen was obtained from a patient with type I pneumococcic lobar pneumonia a strain of influenza B was isolated on first egg passage

(9) J Cl n In st gat on 28 30 318 Ma h 1

human serum U S P and concentrated human gamma globulin moderate the disease picture and probably have a prophylactic effect

[This article is of great interest, not only in suggesting an explanation of acute respiratory disease in newborn infants but possibly also in providing an explanation of certain cases of fibrosis or other damage of the lungs of uncertain origin. It seems probable that some cases of disabling pulmonary fibrosis and emphysema may date back to obscure viral or bacterial infections in infancy At times a congenital structural defect has been suggested but seldom substantiated by objective evidence —Ed.]

PULMONARY DISEASE WITH EOSINOPHILIA

Eosinophilic Respiratory Syndrome Review of 100 Cases The cases reviewed by E Soysa (British Military Hosp Colombo Ceylon) are those of a bronchopulmonary syndrome characterized by spasmodic bronchitis and asthma associated with distinctive blood changes and chest x ray findings and a specific response to arsenic In 70 per cent of the patients a progressive three stage course started with malaise fever and anorexia and insidiously progressed to febrile coryza accompanied by dry cough This phase lasted a week to a month The intermediate stage varied from one month to three years and began with low fever slight splenomegaly and increasing frequency persistence and intensity of cough Most patients gradually became afebrile but continued to have spasmodic bronchitis The terminal or asthmatic stage was the most prominent and affected all but three patients In 70 per cent expiratory dyspnea followed bronchitis and in 25 per cent the illness began with asthma which was sometimes sudden in onset Cough was unproductive in about 15 per cent copious expectoration was rare but sputum was usually scanty and of thick tenacious mucous character Fever and splenic enlargement were less evident than in the preceding stage Duration of this stage was 1 week to 13 years

( ) J R Army M Corp 9 1 3 Jan ry 1949

terial invasion The mechanism by which general host resistance is lowered is not known

[Some investigators suggest that viral infection by damaging the bronchial mucosa may break down important defenses against bacteria and help to open the way for the development of bacterial pneumonias a very plausible assumption—Ed]

Congenital Pneumonitis in Newborn Infants *John M Adams*[1] (Univ of Minnesota) observed three epidemics of upper respiratory tract infection in mothers followed by primary atypical pneumonia in their newborn infants Several mothers had evidence of upper respiratory tract infection at time of delivery or shortly thereafter suggesting that a common agent was responsible for the two seemingly different infections Pharyngeal epithelium of both mothers and babies contained many cytoplasmic bodies typical of virus inclusions

In the first two epidemics 62 per cent of infants had characteristic symptom patterns of cough dyspnea and cyanosis Pneumonitis does not develop in all babies sneezing and coughing were the only symptoms in some Fever if any was moderate Mortality was correlated with severity of symptoms and signs being 20 per cent in the first two epidemics The disease is confined almost entirely to the neonatal period premature babies are very susceptible and have an extremely high mortality rate

Diagnosis is made from symptom patterns and roentgen visualization of generalized increased bronchovascular markings with or without localized areas of increased density Pharyngeal smears show almost complete absence of bacteria and leukocytes but many epithelial cells some of which contain cytoplasmic inclusion bodies In epithelial structures of lungs and tracheas of infants who died typical cytoplasmic inclusion bodies were observed

In treatment of the primary infection sulfonamides and penicillin are valueless Oxygen administered continuously is of great benefit If given early normal

(1) Am J D Child 75 544 554 Ap 1 1948

tory symptoms were controlled by the end of the first week chest x rays appeared normal in two to four weeks and leukocyte counts were within normal limits by the sixth or seventh week Relapses occurred in eight patients but all responded satisfactorily to arsenic

[Viswanathan (Quart J Med 17 257 2 0 October 1943) believes that pulmonary eosinophilosis has been established as a separate clinical entity He thinks it is probably due to an infection and not necessarily to a mite infestation He admits the possibility of a virus infection transmitted by mites and recognizes its resemblance to atypical pneumonia in some respects a high titer cold agglutination may be found in both conditions Smith (J Path & Bact 60 489 494 July 1948) describes an atypical case of this general character which terminated fatally the lesion resembled those of polyarteritis nodosa Cartwright (Am J Med 6 259 266 February 1949) describes a case of the same general category occurring in a patient with clonorchiosis due to the Oriental liver fluke It must be considered in the light of such varying reports that the etiology is not determined there may be multiple causes with similar tissue reactions —Ed]

Tropical Eosinophilic Asthma Report of Two Cases Israel Fond and Paolo Ravenna[3] (Chicago) record the fourth and fifth cases of this disease to be reported in this country All have occurred among United States military personnel returned from the South Pacific area but the disease will probably be recognized outside the veteran population since it is endemic in Cuba and other nearby tropic and semitropical regions Various infestations have been reported in association with tropical eosinophilic asthma but its etiology is unknown since their elimination has been ineffective in control

Onset is gradual with malaise low grade fever paroxysmal coughing and wheezing worse at night or early morning Occasionally the spleen is palpable After a few weeks the temperature returns to normal the spleen is not palpable but paroxysmal coughing and wheezing persist for years

The leukocyte count may be as high as 64 000 with as many as 84 per cent eosinophils and bone marrow is generally active Sputum is usually scanty and seromucous and may contain eosinophils in high percentages

(3) A h I t M a 8 4 430 mb 1948

Characteristic x ray changes were prominent between the second and sixth months and uncommon in initial and late stages Widespread accentuation of finer lung markings and diffuse bilateral ill defined discrete nodular opacities were seen The latter may be differentiated from miliary tubercles by the even symmetrical distribution smaller size and less clear definition More than 50 per cent of the chest x rays had the characteristic appearance but in some instances hilar shadows often showed accentuated density and occasionally one lung field was more affected than the other

The most constant pathologic feature was eosinophilia but severity of symptoms was not proportionate The total leukocyte counts ranged from 10 000 to 70 000 with 10 to 85 per cent eosinophils

Sputum from 67 patients was examined and in 47 samples one or more of four genera of acarian mites were recognized Environmental and occupational circumstances of about 60 per cent of the patients could have exposed them to inhalation of airborne mites from a heavily contaminated atmosphere There was no mite infestation in 13 control patients with respiratory disorders not associated with eosinophilia 17 healthy patients exposed to an atmosphere heavily contaminated with mites and 14 healthy persons selected at random While airborne mites are not usually present in sputum of tropical inhabitants they may infect respiratory passages of susceptible subjects causing asthma and bronchitis with *eosinophilia*

Most patients were treated with carbarsone® leucarsone® or stovarsol® in doses of 1 tablet twice daily after meals Asthma improved most strikingly in patients in whom arsenic provoked a severe initial exacerbation and in those with massive eosinophilia Patients with mild cases usually responded slowly to arsenic orally but one or two supplementary intravenous injections appeared to accelerate the response Adequate total dosage varied between 10 and 20 0 25 Gm carbarsone® tal espira

is recommended because a patient in acute respiratory distress will fight the respirator and be made worse Adequate oxygenation will be provided by 80 90 per cent synchrony of the excursions of the machine with the patient s respirations Because of the unfavorable outcome in two cases it is emphasized that therapy be instituted early in the course of attack before irreversible changes or other grave complications set in This maneuver is suggested as an adjunct to well established methods of treatment

[In many cases of severe status asthmaticus the breathing difficulty is explained not only by the bronchial spasm but by accumulation of viscid secretions and exudate which stagnate in the bronchial pa ages and obstruct ventilation In time the patient may become exhausted from his muscular effort to overcome the obstruction The favorable effect of the respirator may well b explained by the substitution of an artificial mechani m to replace muscular effort at least in part and thus combat the state of exhaustion In some cases the use of intermittent positive pressure breathing such as that advocated by Motley (Am J Med 5 853 856 December 1948) might also be helpful —Ed]

Intravenous Use of Fluids in Bronchial Asthma According to John M Sheldon[5] (Univ of Michigan) use of dextrose is indicated for patients in severe status asthmaticus who do not tolerate fluids given orally or for tho e in whom fluids given orally reflexively produce more severe asthma Lost body water is replaced positive water balance results and needed calories are supplied A 5 per cent solution of dextrose in distilled water is preferred because both water and calories are supplied in isotonic form The patient s dehydration determines the quantity to be given but in general it need not be over 3 000 cc /24 hours

Dextrose is superior to isotonic saline since there is evidence that sodium chloride makes asthma worse Adequate hydration and even stored water in ti sues have no adverse effect on patients with asthma Patients in status asthmaticus must be kept well hydrated even if this must be done intravenously

Contraindications to intravenous use of dextrose are

5 J A M A 139 506 507 Feb 19 1949

Chest x rays in the early stages show diffuse fine mottling of pulmonary fields which disappears after three to four weeks Later in the disease bronchial shadows may be widened Often the x ray picture of the chest is normal

Specific treatment is provided by arsenicals whose mode of action is unknown In evaluating any theory it is important to remember that the amount of arsenic used is small and that complete recovery precedes by months the return of leukocyte counts to normal Neoarsphenamine is given intravenously in doses of 0 1 0 30 0 45 0 45 and 0 45 Gm doses at five day intervals

Both of the authors patients had typical history physical and laboratory findings although they had been treated for bronchial asthma for many years Response to neoarsphenamine intravenously was prompt and typical in each instance

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BRONCHIAL ASTHMA

Observations on Use of the Respirator in Refractory Status Asthmaticus According to Morton F Reiser and Eugene B Ferris Jr[4] (Univ of Cincinnati) a small number of patients with acute intractable asthma fail to respond to the most heroic and carefully planned therapy In these the chest and lungs are maximally expanded and the primary difficulty is in expiration In such cases use of the Drinker respirator is of value because it applies positive pressure to chest wall and abdomen thus supporting the expiratory phase Because the respirator also aids inspiration inspiratory dyspnea is at the same time decreased

In three patients application of mechanical energy for support of expiration caused prompt dramatic disappearance of cyanosis and relief from anoxia with improvement in circulation Induction of partial anesthesia

(4) A Int M d 29 64 70 J l 1948

degrees of severity The mimicry of extrapulmonary *tuberculosis is notorious as is the 50 per cent case fatal* ity Among white adult males approximately 1 in 580 of those infected and 1 in 100 with clinical disease undergo



F g 48 —D l pm t f oc l dal ca t f p eum nt I filt tio ght b th d y ft t S d m t 25 mm (C t y f Sm h C E A J t M d 9 623 655 O t be 1948)

extrapulmonary dissemination Dissemination is much less frequent in females It usually occurs soon after in fection is acquired frequently within weeks and infre quently after months Once it ensues the risk of its con tinuance is great even though remission may occur

few A weakened myocardium is jeopardized by the rapid increase in blood volume which the osmotic action of dextrose produces Speed shock occurs especially when hypertonic solutions are used In some patients with angina pectoris this therapy may cause pain These objections may be minimized if the solution is given at a *rate not exceeding 500 cc /hour*

[The principles advocated by Sheldon seem to be quite rational Obviously one should be sure that one is dealing with true bronchial asthma and not cardiac asthma in which administration of quantities of fluid might be contraindicated also consideration should be given to the possible existence of chronic pulmonary emphysema with or without fibrosis in a patient with asthmatic symptoms In such circumstances sustained strain might be imposed on the right heart and might be aggravated by an increase of circulating fluid However many clinicians know that uncomplicated bronchial asthma does not lead to heart failure Andre Cournand in his cardiorespiratory laboratory in Bellevue Hospital has measured the pulmonary arterial pressure in two patients during an acute attack of bronchial asthma In one the pressure was not perceptibly increased and in the other the increase was very slight and was explained by presence of pre existing pulmonary emphysema *This helps to explain the mechanisms involved in asthma* and their significance with respect to treatment —Ed]

FUNGUS INFECTIONS

Pathogenesis of Coccidioidomycosis with Special Reference to Pulmonary Cavitation Charles Edward Smith Rodney Rau Beard and Margaret Taiko Saito[6] (Stanford Univ) state that human infections of Coccidioides immitis are usually acquired by inhaling chlamydospores and arthrospores of the fungus Pneumonic or *respiratory symptoms occur with varying severity in 40* per cent of infected patients Erythema nodosum pleural effusion pulmonary cavitation and spontaneous pneumothorax or hydropneumothorax are complications of primary infection They may be confused with the progressive or disseminating form coccidioidal granuloma

Disseminated progressive or secondary coccidioidal infection is evident clinically in any or all organs in all

(6) Ann Int Med 29 3 655 October 1948

have never seen dissemination in a patient with coccidioi dal cavitation

Amon 753 patients with coccidioidal disease cavities were detected in 13 (1 7 per cent) Because incidence

Fig 50 — S m h w g f lly d l p d ty w k f t S d m at t 4 m (C t y f Sm th C E t l A I M d 29 623 655 Oct be 1948)

of cavitation in inapparent infections cannot be esti mated it should be emphasized that these figures apply only to 25 40 per cent of the infections with manifest symptoms Of 274 patients with pulmonary cavities due to coccidioidal infection diagnosis was established

Coccidioidal pulmonary cavitation is not in the category of disseminating or progressive coccidioidal granuloma Cavities may develop early in the course of primary illness often beginning in the pneumonic lesion a



Fig 49—S me a sh w ng b g g c v t t on tw w k lat r S d mentat n rate 19 mm (C t y of Sm th C E *et al* A n I t Med. 29 6 3 655 October 1948)

week or two after onset (Figs 48 50) Or pneumonic areas may become smaller and the patient may be completely over clinical illness when an excavation develops and a cavity rapidly forms Immunologically only in rare cases is the infection seriously active The authors

ment fixation tests are in striking contrast to the high titer observed in disseminated coccidioidal infection Often the etiology of a suspected coccidioidal cavity can be established only by recovery of the fungus In nearly 75 per cent of patients with coccidioidal pulmonary cavities the sedimentation rates were normal in direct contrast to the accelerated rate in initial illness or progressive coccidioidal granuloma

Few coccidioidal cavities menace health or activity They are likely to remain open In this series 82 were open at least 6 months 72 over 1 year 37 over 2 years 25 over 3 years 14 over 4 years and 3 over 10 years Only 31 were reported to have closed 12 within six months and 22 within a year Unless there is repeated hemoptysis or troublesome coughing or chest pain the patient may be left alone Coccidioides in the sputum does not pose a public health problem

In 6 of the group closure of a cavity followed pneumothorax treatment but in 10 patients this failed Contraindications to this method are subpleural cavity and danger of bronchopleural fistula or spontaneous hydropneumothorax Phrenic crush closed at least four cavities in this group but six patients were not benefited by it If cavitation develops during initial infection strict bed rest should be continued even after temperature and sedimentation rates are normal With old cavities bed rest alone has rarely proved useful When more conservative measures fail lobectomy pneumonectomy or segmental resection is recommended Controlling bacteria with antibiotics results in uncomplicated healing Dissemination and local spread of coccidioides can be avoided if bacterial infection is controlled

[This excellent article demonstrates the relative mildness of coccidioidal cavities In this sense they differ from tuberculous cavities which are frequently the source of dissemination of infection into healthy parts of the lungs However in areas surrounding coccidioidal cavities histologic examination sometimes shows minute lesions which did not undergo extensive necrosis but became localized and organized Practically speaking as the authors suggest a patient with a coccidioidal cavity but no symptoms may be ob

by positive cultures in 40 per cent positive serology in 49 per cent and positive coccidioidin with negative tuberculin test in 11 per cent A possible pitfall in diagnosing etiology of cavitation may be infection with both Mycobacterium tuberculosis and C immitis seven such cases are included in this group Proof of one infection may end studies which would have revealed the other

The benign nature of most coccidioidal cavities is notable The outstanding symptom produced by cavitation was hemoptysis It was rarely sufficient to menace health but nearly 60 per cent of civilian cases were detected because of it Chest pain cough malaise fever or excessive sputum accounted for only 10 per cent of military and civilian discoveries

In 269 patients the number of cavities could be noted Single cavities occurred in 90 per cent multiple cavities in 6 per cent and multilocular cavities in 4 per cent They were located in the upper chest in 70 per cent and in the lower in 30 per cent Apical cavities were noted in 12 per cent of the group

The first step in diagnosis of coccidioidal infection is application of a coccidioidin skin test Strong reaction does not activate or disseminate the infection nor does it complicate diagnosis by stimulating diagnostic precipitins or complement fixing antibodies When concentrations greater than 1 100 are used nonspecific cross reactions may be confusing especially in reactors to histoplasmin Readings should be made at 24 and 48 hours Induration over 5 mm should be read as positive at either period Precipitin and complement fixation tests are also useful in diagnosis Both tests are generally negative in mild inapparent coccidioidal infections The precipitins appear before complement fixing antibodies but if the latter do appear they generally persist longer Usually precipitins disappear a month or two after infection has been acquired The complement fixation test of serum provides an important diagnostic aid In cavity cases negative equivocal or low titer comple

pig inoculations for acid fast bacilli were negative She lost weight and became increasingly ill Biopsy of a small firm cervical lymph node on Jan 1 1947 revealed numerous large macrophages containing typical *Histopla ma cap ulatum*

She was transferred to a general hospital On admission she was emaciated and coughed intermittently temperature was 100 F pulse rate 134 and respiratory rate 20 There was *evidence of massive involvement of right lower lung field and*



Fig 51—Ch t film A g 3 1946 (Cou te y f Dubl W B l l Am. R T b 58 56 570 N mb 1948)

liver and pleen were enlarged Leukocytosis varied from 15 000 *to 30 000 most cells being neutrophils Skin tests with* histoplasmin and complement fixation tests using heat killed antigen or concentrated histoplasmin filtrate were repeatedly negative When a citrated blood specimen was allowed to stand in the dark *for two weeks at room temperature colonies of the* organism could be seen Specimens of pleural fluid placed on Sabouraud s medium at room temperature yielded the organ ism In all cultures typical tuberculate chlamydo pores were identified *The patient became progressively weaker and died* February 8 Autopsy revealed a fibrocaseous granulomatous

served by x ray examination every three to six months with the expectation that no serious progression of the disease will occur —Ed]

Surgical Treatment of Pulmonary Coccidioidomycosis (Local Excision of Small Lesions) Greer Forsee and Mahon consider pulmonary resection indicated in coccid ioidomycosis when there has been recurrent moderate hemoptysis failure of cavity closure after many months observation or spontaneous pneumothorax with failure of the lung to re expand and to exclude neoplastic dis ease Dermont W Melick[7] (Phoenix) carried out success ful pulmonary resections on two patients one with a cavity in the right upper lung for many months and 35 small pulmonary hemorrhages and the other with a small nodular lesion at the periphery of the left upper lobe which it was thought might be a neoplasm

Unless the lesion is small and located peripherally lobectomy or segmental resection rather than local ex cision should be carried out

[As indicated in the preceding article surgery does not seem to be indicated in these cases unless untoward symptoms develop In one case reported by Krapin and Lovelock (Am Rev Tuberc 58 282 290 September 1948) new cavities developed some months after a presumed solitary cavity was removed by lob ctomy —Ed]

Histoplasmosis A case of generalized histoplasmosis is reported by William B Dublin Clyde G Culbertson and Herbert P Friedman[8] (Indianapolis)

Woman 21 without subjective complaint was directed to consult a physician on Aug 3 1946 after a survey chest x ray revealed a pulmonary lesion She had lost 5 lb during the pre ceding month and physical examination showed diminution *of breath sounds dulness and medium and fine rales in* the lower part of the right lung A chest x ray showed infiltration in both lungs especially the right inferiorly the right lung showed an area of conglomerate nodules 5 cm in diameter The hilar nodes were greatly enlarged Repeated sputum ex aminations failed to yield acid fast bacilli On September 5 a chest x ray showed definite bilateral progression of the lesions A histoplasmin skin test was negative Because of a family hi tory of tuberculosis the patient was admitted to a sanatorium where repeated sputum examinations and guinea

(7) Arizo M d 6 4 Ap 1 1949
(8) Am R v T be 58 562 570 Novembe 1948

passed in feces or less commonly escapes via ulcerated skin If it reached water within a few weeks miracidia are hatched which penetrate snails of several species Several months elapse for transformation of miracidia through stages of sporocysts rediae and cercariae Cercariae invade the second intermediate host a crustacean (either crab or crayfish of many species) and encyst in the muscles as metacercariae Following ingestion of raw or incompletely cooked infected crab or crayfish these are released in the alimentary tract and penetrate the jejunal region The peritoneal cavity is entered the diaphragm invaded and eventually the lung *where most parasites mature Encystment may* occur and eventually eggs may be found in the cyst or parenchyma of the lung At autopsy infection may involve almost every organ

Clinically the patient shows a slowly progressive pulmonary disease In this series all but one patient had eaten fresh water shellfish Cough or hemoptysis gradually increasing in severity was the first symptom in all patients The cough was at first dry and irritating but rapidly became productive Sputum characteristically contained flecks of dark blood but tenacious thin watery yellow white sputum was frequently seen The amount varied from 30 to 90 cc per day Dark greenish sputum was encountered only in patients with associated tuberculosis Chest pain loss of weight weakness and tiredness were common complaints

Despite the histories and symptoms most patients did not appear to be sick In only two did temperature exceed 102 F during hospitalization Physical signs of pulmonary disease were present in all

Laboratory diagnosis depends on recognition of characteristic ova in sputum feces fluid of serous cavities or broken down infected lymph nodes Scattered brownish red flecks closely resembling cigaret tobacco shreds in sputum are especially indicative of accompanying ova Ova are easily identified when seen but staining will

process with numerous macrophages containing typical H capsulatum The lesions appeared massively in lungs liver spleen lymph nodes thymus and vertebrae and infrequently in virtually every organ except the central nervous system

Histoplasmin skin tests are of greatest value in epidemiologic studies in connection with primary or sensitizing infections In persons with late disseminated histoplasmosis the skin test may be negative Strong filtrates are irritating and produce reactions in nonsensitized animals so that use of filtrates which yield an excessive percentage of positive tests in a given community is not recommended

[The clinical resemblance of this condition to atypical tuberculosis creates an important practical problem In such situations if the patient i expectorating purulent sputum caused by tuberculosis a careful and intensive search should quickly reveal tubercle bacilli Failure to find them should immediately suggest some other type of infection and the various myco es should be considered The tuberculin test is helpful only when no reaction occurs Progressive histoplasmosis is seldom diagnosed particularly in its early phase and there is no reliable information concerning the possible effectiveness of various antibacterial agents —Ed]

PARAGONIMIASIS

Pulmonary Paragonimiasis Alvin J B Tillman (New York City) and Harry S Phillips[9] (Westport Conn) observed 12 cases of paragonimiasis in Filipinos on the island of Leyte The disease may simulate tuberculosis so closely that it should be considered in differential diagnosis of hemoptysis in persons in endemic regions India Africa Central China French Indo China Manchuria Samoan Islands Malay Peninsula New Guinea and South America Infected cats dogs and other animals have been discovered in Ohio Minnesota Wisconsin California South Carolina Mississippi New York and Kentucky

Paragonimus westermani like all trematodes has a complex life cycle The egg is coughed up in sputum

(9) Am. J Med 5 167 187 A gu t 1948

Involvement of the lung in the first chest x ray was found in 11 patients In six patients involvement was massive and large areas of density were present In five changes were diffuse and lesions were small soft and generally multiple (Fig 52) Right lung and lower lobe were more frequently affected than left lung and upper lobe Massive lesions had no discernible specific characteristics which suggested the presence of paragonimiasis Diffuse small lesions believed to be strongly suggestive of this disease may be simulated by early pulmonary lesions of Schistosoma japonicum infection Therapy caused disappearance of shadows in only one case

Because patients were observed for only a few months end results of treatment are not recorded Emetine hydrochloride given intramuscularly in divided doses which totaled 0 3-0 36 Gm gave definite subjective relief in a short period in nine patients After a lag sputum and frequency and severity of the cough decreased There was no apparent relation between duration of symptoms and effect of emetine on disappearance of ova In 11 cases sputum and pleural fluid were negative at conclusion of observation Several courses of emetine were administered in all but one remaining positive patient who had only one course

To establish diagnosis of paragonimiasis recovery of ova is imperative However features of the disease previously outlined aid in diagnosis and lead to a more intensive search for ova Bizarre multiple lesions seen by chest x ray should focus attention to possibility of parasitic infection Normal lung x rays in presence of hemoptysis and a history of sojourn in an endemic region should direct attention to possibility of paragonimiasis

[Some clinicians advise the use of sulfadiazine in addition to emetine on the assumption that there may be an associated bacterial infection in some of the lesions In this connection reference may be made to pulmonary lesions caused by another Oriental fluke Clonorchis sinensis described by Ca t v ght (Am J Med 6.2 9 66 February 1949) —Ed]

mask their presence They are not produced in sputum regularly and in quantity so examination of many specimens is required before it can be assumed they are absent The average hemoglobin (Sahli) prior to therapy was 83 per cent average erythrocyte count 4 300 000/cu



F g 57—Ch cte t l s of p lm na y pa g m s (Co t sy f T llma A J B nd Ph ll p H S Am J M d 5 167 187 A g st, 1948)

mm and average leukocyte count 11 300/cu mm Most authors state that paragonimiasis is not accompanied by eosinophilia Although erythrocyte sedimentation rate was elevated above 20 mm /hour in 10 patients the data do not permit thorough evaluation of its significance in this disease Transiently positive serologic tests were noted in four patients Urinary findings were normal in all

nary arterial system At each point the bronchial artery is of the same size or slightly smaller than the pulmonary twig which it joins suggesting a much greater blood supply from bronchial vessels than from pulmonary arteries when greater pressure impelling the blood in the former is considered

At least three changes occurred during the develop

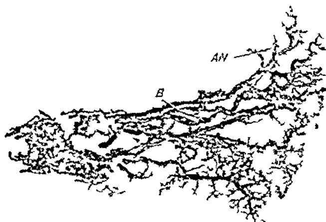
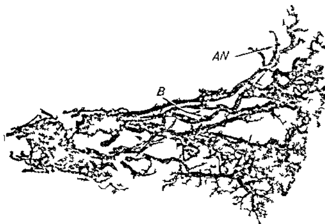


Fig 53—R [illegible] d [illegible] f th [illegible] b [illegible] y t m f m p lmo na y art [illegible] al b [illegible] f b p lm [illegible] h w [illegible] R th su [illegible] bo [illegible] h [illegible] hal rt y (B bel w spe most pulm ry b [illegible] Th b [illegible] hal [illegible] g [illegible] (A) w th th [illegible] leat w [illegible] f th pulm Red d f m [illegible] (C [illegible] L bow A A [illegible] Am J P th 25 11 31 35 [illegible] 1949)

ment and after establishment of bronchiectasis which could not exist without an increased supply of oxygenated blood from the aorta The most significant is organizing pneumonitis which usually precedes bronchiectasis (Fig 54) At that time newly budding capillaries supplying oxygen to the granulation tissue may be derived from both systems and these may join Since pulmonary and bronchial trunks are immediately adjacent some of the larger capillary channels may bring them

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F g 53—R t g d j t f th b n h l t l y t m f m p lm y t l b h t th p lm y t y h w t m t g th j bor g f h N t b h l t y (*B*) b l w pp m t p lm y b h Th b h l a t y b i g tom (*A*) w h th b h d l t tw th b h of th p lm t R d d f m y (C y f L b w A A *t l* Am J P th 5 211 31 M h 1949)

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Enlargement of Bronchial Arteries, and Their Anastomoses with Pulmonary Arteries in Bronchiectasis Averill A Liebow Milton R Hales and Gustaf E Lindskog[1] (Yale Univ) prepared 18 specimens of lungs removed surgically from patients with bronchiectasis as casts by the Vinylite corrosion technic Striking bronchial arterial enlargement and anastomoses with the pulmonary artery were found in 15 As shown in Figure 53 the arterial system appeared at least doubled and often many times compounded for each branch of the respiratory tree in contrast with simple arborization of the normal pulmonary arterial tree where a single branch follows the course of each bronchus or bronchiole

Pulmonary arteries pursue a rectilinear course roughly parallel with respiratory tree branches but bronchial arterial trunks take a spiral course in relation to the long axis of each bronchus Pulmonary arteries are truly end arteries and communications exist only among finer capillary networks In contrast even larger bronchial vessels especially in bronchiectasis are arranged in a dense communicating network and often communicating branches are as large as trunks which they unite So numerous are sources of collateral supply that ligation of larger identifiable bronchial arteries at their sources is always defeated by an immediate overgrowth of accessory vessels

No anastomoses were found proximal to third order bronchi in the segments and in most instances they were first found along branches of the fourth order in relation to walls of large bronchiectatic sacs Additional anastomoses usually multiple and large were often found far beyond the last injected sac (Fig 53)

Usually bronchial artery plexuses around a single bronchus communicate at many points with the pulmo

(1) Am J Path 5 11 211 March 1949

editor's attention. It brings out important information concerning the pathogenesis of bronchiectasis and helps explain for instance the frequency of hemoptyses which most often seem to be due to breakdown of vascular granulation tissue in the wall of the diseased bronchus —Ed]

Prospects for Prevention of Chronic Bronchitis and Bronchiectasis Rational Management of Bronchopulmonary Infections by Penicillin Aerosol Therapy Primary pyogenic respiratory infection as in laryngotracheobronchitis (frequently due to intrafamilial chronic respiratory infection) pertussis and bronchopneumonia secondary to measles or influenza are important factors in bronchial suppuration with subsequent bronchial obstruction and atelectasis These reversible changes may lead to chronic bronchitis pulmonary fibrosis with emphysema or bronchiectasis Recognition and eradication of the initial infection at the earliest possible stage prevent chronic pulmonary disease According to Walter Finke (Univ of Rochester) penicillin aerosol is the best treatment but to insure permanent cure of even the mildest conditions patients should be followed closely so that relapses may be treated before new damage to the respiratory system occurs

In chronic conditions prognosis is less favorable With improvement of general health penicillin aerosol bronchoscopic aspiration of secretions and systematic postural drainage may lead to arrest

A simple bicycle pump can be used if a glass fiber filter is inserted between pump and one of the nebulizers usually recommended for adults Since many children prefer to inhale through the nose and exhale through the mouth rather than vice versa a nasal adapter is used

Large doses of penicillin given initially are most effective in eliminating active infection In Finke's patients respiratory symptoms disappeared within one or two weeks unless the condition was advanced In advanced conditions 100 000 units of penicillin was administered once or twice daily In mild cases one daily inhalation of

(2) J Ped 1 33 29 4 J ly 1948

into communication These channels may persist after organization is complete The second change is the pronounced hypertrophy of bronchial smooth muscle that occurs in expanded bronchial walls in some cases of bronchiectasis The third is the increase in lymphoid tissue which may form huge follicles both in walls of sacs and in large proximal bronchi

Bronchial and pulmonary artery anastomoses account partly for the minimal desaturation of systemic arterial



Fg 54—Ab ndant v s ular g a l t o t s ue le at g the p do tr t h d el t d co omn r p t l m that l c a b o ch tat c a c Redu ed f om × 50 (Cou tesy of Li bow A A t l Am J P th 25 211 31 March 1949)

blood even in severe bronchiectasis The pressure in pulmonary arteries that enter diseased tissue is increased by their communication therein with branches of systemic circulation Thus, pulmonary arterial blood is shunted away from anastomoses into healthy parenchyma capable of more efficiently oxygenating the contained venous blood In severe bilateral bronchiectases when no more than a relatively small amount of intact pulmonary substance remains the high pressure transmitted from anastomoses may contribute to pulmonary hypertension and ultimately to development of cor pulmonale

[This is the best study of this character wh ome to the

editor's attention It brings out important information concerning the pathogenesis of bronchiectasis and helps explain for instance the frequency of hemoptyses which most often seem to be due to breakdown of vascular granulation tissue in the wall of the diseased bronchus —Ed]

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(2) J. Ped 33 242 July 1948

50 000 units was sufficient to control infection once it had subsided Treatment was discontinued gradually and resumed immediately if respiratory symptoms re appeared Side effects severe enough to cause discon tinuance of penicillin were not encountered

Response to penicillin was prompt and improvement great in all but 1 of 15 patients followed one year or more Mild relapses occurred in nine and severe relapses in one Five tended to relapse when treatment was dis continued

It should be emphasized that bronchopulmonary infec tion is common and apparently communicable and is a public health problem Public enlightenment about pro phylactic measures and greater knowledge among phy sicians will stimulate individual efforts to prevent chronic bronchitis and bronchiectasis

[It is certainly logical to prevent severe respiratory infections among children and clear up those which do occur as soon as possible in the hope of avoiding irreversible damage It is generally agreed that mild self limited infections do not require the use of antibiotics which should be reserved for more serious attacks penicillin aerosol should be used with discretion Bronchoscopic aspiration of secretions is of questionable value and is seldom necessary if other measures are used in an adequate manner —Ed.]

Honeycomb Lungs Neville Oswald and Thomas Park inson[3] (London) studied 16 patients with thin walled cysts distributed uniformly throughout both lungs The cysts varied in size up to 1 cm in diameter In six the disease was associated with xanthomatosis tuberous sclerosis and allied disorders biliary cirrhosis or pitui tary disorder Similar associations have been reported previously but the nature of the pathologic changes re sponsible for these combinations has not been determined

In six patients aged 7 24 honeycomb lungs were as sociated with spontaneous pneumothorax (Fig 55) Four aged 25 55 presented right heart failure but none had a history of spontaneous pneumothorax This suggests a difference in the nature of the cystic disease in the two age groups

(3) Quart J Med 18 1 9 January 1949





Fig 55 (top) —H y t pp d g p t ɾ eu h
Fig 56 (b tt m) —S t f wh l l g h w g f d t b t n f
(C t y f O w ld \ y i P k d w bɾleu l b ll T Q t J M d 18 1 0 J
y 1949)

All patients with right heart failure died and autopsy revealed a strikingly similar picture Normal lung structure was largely replaced by air-containing cystic spaces varying in size from just visible to about 1 cm (Fig 56) They were separated by thick fibrous septa consisting of dense collagen and blood vessels Between the septa were irregular areas of relatively normal lung with polymorphonuclear infiltration throughout the interstitial tissue Some cyst spaces were lined with flat epithelium and others had no lining There was no evidence of bronchiolar obstruction In cases of tuberous sclerosis and allied disorders there is proliferation of smooth muscle as part of the diffuse interstitial infiltration and in xanthomatoses lipoid cell granulomas

Eight patients had spontaneous pneumothorax and eight had progressive dyspnea both of which are characteristic of honeycomb lungs regardless of etiology X ray diagnosis depends on identification of cysts throughout both lungs reticulation and a normal bronchial tree The cysts are often best demonstrable behind the sternum in a lateral film or in a tomogram

Etiology of widespread alveolar cysts is unknown They may arise as a developmental abnormality or secondary to mechanical factors resulting from acquired disease In most cases not associated with general medical disorder inflammation suggests an inflammatory origin Acute infections either after influenza measles or whooping cough or in the absence of a precursor may affect predominantly the smaller radicles of the bronchial tree When infection leads to obstruction or distortion of smaller bronchi or bronchioles cysts may result from impeded expiration

[As Oswald and Parkinson suggest this condition represents a varying combination of lesions due in all probability to varying causes although the principal one seems to be destructive inflammatory disease occurring most often early in childhood or infancy The main problem is prevention consisting of proper treatment of severe bronchopneumonia Another condition which may be associated with bronchiectasis or honeycomb lung is cystic fibrosis of the pancreas Pugsley and Spence (Ann Int) 1262 1272 June 1949) recently reported such a case —E

Boeck's Sarcoid Observations on Seven Patients, One Autopsy According to Gaylord S Bates and John M Walsh[4] (U S N R) Boeck's sarcoid is not rare but is frequently not recognized All of their patients were young adults and four were Negroes Admission symptoms and physical findings did not suggest the correct diagnosis except in one patient who had what may have been a distinctive skin lesion Its significance was not appreciated until he had returned to duty and no biopsy was taken The wide hilar shadows seen in five patients were regarded as enlarged lymph nodes These shadows are an early and important feature of Boeck's sarcoid Peribronchial mottling seen in the x ray of one patient was interpreted as sarcoidosis of the lung parenchyma

In diagnosis laboratory procedures were most helpful in excluding diseases for which specific tests are available Elevated serum protein value with hyperglobulinemia observed in two patients may prove to be a constant feature of sarcoid Sedimentation rate was above normal in five patients at time of admission and remained so for varying periods Lymph node biopsy is important and usually accurate in diagnosis of this disease If necessary it should be repeated without hesitancy The characteristic histologic lesion was found in lymph nodes removed from each of the seven patients

In the one patient who died autopsy disclosed widespread distribution of noncaseating tubercle typical of sarcoid in the myocardium including the interventricular septum and the epicardium A review of the patient's record disclosed that he had maintained a pulse rate of 90 120 even when afebrile Persistent tachycardia should not be ignored for it may indicate myocardial involvement which may result in unexpected death

[The potential seriousness of sarcoidosis is generally underesti

[4] I t M d 9 306 317 A gust 1948

mated because the pulmonary lesions often subside spontaneously There is a definite possibility of progressive disabling disease On this account when the condition is diagnosed at or near its inception rest treatment would seem to be rational in view of the lack of any specific therapy The purpose obviously would be to favor the increase of nonspecific resistance against a disease which appears to be due to some infectious agent—Ed]

Tuberculin Neutralizing Factor in Serum of Patients with Sarcoidosis A Q Wells and J A H Wylie[5] (Oxford Univ) found that serum of patients with sarcoidosis can modify or neutralize the ability of old tuberculin (OT) to cause a typical reaction in skin of hypersensitive persons The phenomenon is occasionally observed with apparently normal serums and with those from patients with diseases characterized by mobilization of epithelioid cells such as kala azar Occasionally serum from a patient with sarcoidosis does not neutralize OT, especially after treatment The test is unsuitable as a routine diagnostic procedure for these reasons

The neutralizing factor seems to be present in greater amounts or more potent when the sarcoid process is active The same serum when used in patient with active progressive tuberculosis is less effective than when used in persons without active tuberculosis Because berylliosis may sometimes be confused with sarcoidosis it would be of interest to know if the serum from those with berylliosis possesses neutralizing properties

Electrophoretic fractionation has disclosed that the tuberculin neutralizing power is in the gamma globulin Normal human gamma globulin shows no such activity

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PNEUMOCONIOSIS

Aluminum Therapy in Advanced Silicosis John W Berry[6] (Denver) reports experiments to determine if inhalation of aluminum powder is of value in silicosis treatment Animal experiments published in 1937 showed

(5) Lancet 1 439 441 M 1 1949
(6) Am. Rev Tube 57 55/ 57 J 1948

that aluminum powder caused regression of immature silicotic nodules A gelatinous aluminum hydroxide coating was formed about silicon particles Several years later this treatment was reported valuable in human silicosis and since then many articles published have implied that patients with silicosis were relieved of symptoms by administration of aluminum Berry feels these studies were not satisfactorily controlled

In this study 35 men with silicosis were placed in a room into which air was blown by a specially designed machine Fine aluminum particles in a concentration of 1 mg cu ft were blown into the room while 26 of the patients were treated and air without aluminum was blown into the room while 9 control patients were studied Massive conglomerate lesions were present in 96 per cent of patients and discrete nodulation in 4 per cent Average time since last exposure to silicon in the treated group was 3 2 years and in the control group 4 4 years Treated patients were exposed for an average of 96 days and controls 55 days

Results of therapy were evaluated chiefly by estimation of disability dyspnea chest pain cough and sputum In all categories more improvement was found in controls than in those treated with aluminum All 35 patients thought they were receiving the same therapy

In the aluminum treated group no objective changes were observed which could be attributed to metallic therapy Although no definite conclusions were made because of the small group studied Berry suggests that the good results previously reported might be only psychologic

[This study will probably put a stop to the use of aluminum at least until more experimental work has been completed Inhaled aluminum dust may not be entirely innocuous There is often an element of anxiety in the silicotic patient which colors his subjective symptoms and his apparent response to treatment —Ed]

Pneumonitis and Granulomatosis Peculiar to Beryllium Workers Frank R Dutra[7] (Univ of Cincinnati) states that granulomas in skin and subcutaneous tissue into

( ) Am J P th 4 1137 1165 N mbe 1948

which beryllium oxide has been introduced accidentally are similar to those in the lungs and provide further proof that beryllium is pathogenic in contact with living tissues Tissues from 7 persons who died of acute pneumonitis and from 13 who died of chronic granulomatosis were examined Pathologically differentiation into acute and chronic disease is not clearcut for all stages of transition between them have been seen The designation acute pneumonitis is inadequate since exudate organization not ordinarily considered part of a strictly acute reaction was noted in six of the seven acute cases The designation chronic granulomatosis neglects mention of emphysema and diffuse fibrosis which are more important to the patient s well being and pulmonary function than are granulomas The earliest phase of recognizable granuloma was seen in a patient who died of acute beryllium pneumonitis whereas all well developed granulomas were found in patients with chronic disease

Grossly the lungs in acute pneumonitis were boggy and consolidated whereas in the chronic form they were voluminous and emphysematous

Microscopically the acute cases were characterized by inflammatory exudate and early formation of connective tissue in the lungs There were varying amounts of fluid in alveoli with mononuclear cells and scattered lymphocytes plasma cells polymorphonuclear leukocytes and erythrocytes (Fig 57) In some alveoli desquamated alveolar lining cells coalesced to form giant cells around degenerating and necrotic masses of mononuclear cells In later stages there were proliferation of fibroblasts within adjacent alveolar walls organization of the periphery of the mass and formation of a granuloma with fibrinoid material at its center (Fig 58) In all cases interstitial tissues of septal walls were infiltrated by lymphocytes and plasma cells Fibrosis manifest by early appearance of reticulum in intra alveolar exudate and ingrowth of fibroblasts occurred fairly early in acute pneumonitis

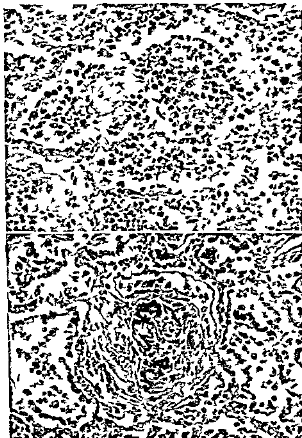


Fig 57 (top) —E d t mp d f l tocyte lymp y d [l ma ll A t p m t R d ced f m × 3 0
Fig 58 (bott m) —W ll t m d g l m pt m ll S p t fib d m t l o d d by l se ll g A t p mont R d d f m × 250
(C rt y f D t F R Am J P th 4 1137 1165 N mb 1948)

Morphologically cases of chronic granulomatosis rep resented a further development of acute pneumonitis Intraseptal lymphocytes and plasma cells were more

which beryllium oxide has been introduced accidentally are similar to those in the lungs and provide further proof that *beryllium is pathogenic in contact* with living tissues Tissues from 7 persons who died of acute pneumonitis and from 13 who died of chronic granulomatosis were examined Pathologically differentiation into acute and chronic disease is not clearcut for all stages of transition between them have been seen The designation acute pneumonitis is inadequate since exudate organization not ordinarily considered part of a strictly acute reaction was noted in six of the seven acute cases The designation chronic granulomatosis neglects mention of *emphysema and diffuse fibrosis* which *are more* important to the patient s well being and pulmonary function than are granulomas The earliest phase of recognizable granuloma was seen in a patient who died of acute beryllium pneumonitis whereas all well developed granulomas were found in patients with chronic disease

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material or a Langhans giant cell They were confined to enlarged septal walls or peritruncal connective tissues Within some granulomas were peculiar basophilic structure identified as conchoidal bodies often found in Boeck s sarcoid (Fig 59) These bodies were seen in 11 of the 13 chronic cases and sometimes were enclosed in the cytoplasm of a giant cell The final stage of the granuloma seen in five cases was a single nodule or coalescence of several nodules which had become completely fibrotic (Fig 60)

In the acute cases bronchopulmonary and mediastinal lymph nodes were hyperemic and contained large mononuclear cells whereas in chronic cases fibrosis granulomas and giant cells were found In one case of acute pneumonitis there was marked centrolobular necrosis of the liver whereas in one of chronic granulomatosis the liver contained granulomas

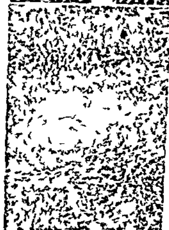
Lesions of acute beryllium pneumonitis are not specific in their earlier phases but after two weeks when the well defined granulomas of chronic granulomatosis appear the lesions are different from those of any other pathologic process Beryllium granulomatosis has been confused with Boeck s sarcoid but the conditions can be differentiated readily by microscopic examination of tissues Analysis of tissue from even cases of typical Boeck s sarcoid has failed to reveal beryllium A history of beryllium exposure and its recovery from urine or the lungs differentiate beryllium pneumonitis from all other conditions

(The respiratory difficulty caused by this condition sometimes described as berylliosis seems to be referable chiefly to the organization of the walls of the pulmonary alveoli interfering with the diffusion of gases across the membrane The work of Bruce and his associates (Am Rev Tuberc 59 364 390 April 1949) and of Baldwin Cournand and Richards (Medicine 28 1 25 February 1949) explain the mechanism and effect of the diffusion difficulty which differs from that of certain other pulmonary fibroses With the history of exposure to beryllium the functional tests help to support the diagnosis of the pulmonary lesions

It is reported that the United States Public Health Service and large industries in which beryllium is a hazard have agreed to measures for its elimination Much newspaper and radio publicity

numerous than were free cells in alveolar spaces Polymorphonuclear leukocytes were virtually absent but there were many Langhans giant cells Emphysema was





F g 59 (abo) —C ch ll bod s O w th a g a t c ll nd th th l s f t d b w th g l m Ch g l mat Re d d f × 3 0

F g 60 (l ft) —M e ad a ced t g of fit of a g n loma f m e f h c g lo m t s R du d f om × 16)

(C t y f D t T P Am J P th 24 1137 1165 N mbe 1948)

extensive and fibrosis in septa granulomas and perivascular and bronchial regions was marked Granulomas consisted of a peripheral zone of loose fibrous tissue surrounding necrotic granular eosinophilic de fibrinoid

berylliosis Thus beryllium in urine is an evidence of beryllium absorption rather than of berylliosis and indicates exposure to beryllium If the substance is found in urine of a patient with pneumonitis the possibility that the lung disease is caused by beryllium must be seriously considered

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CIRCULATORY AND VASCULAR DISTURBANCES

Effect of Patent Ductus Arteriosus and of Interauricular and Interventricular Septal Defects on Development of Pulmonary Vascular Lesions Kenneth J Welch and Thomas D Kinney[9] (Peter Bent Brigham Hosp) studied 67 cases of congenital heart disease in which there was left to right shunt to determine the effect of the altered hemodynamics on the pulmonary vascular bed The lesions were classified under the headings intimal proliferative changes hyaline changes and medial changes Findings in 10 controls for each of the first seven decades of life were compared Incidence of pulmonary atherosclerosis due to aging alone was high even in the third and fourth decades

In all but 1 of 25 cases of patent ductus arteriosus changes in the pulmonary vascular system were no greater than those in controls of comparable age No medial changes were found All changes observed were atherosclerotic in type

There were 25 cases of unguarded interauricular septal defects at least 0 8 cm in diameter In 13 uncomplicated cases the pulmonary vascular lesions were no greater than in controls of the same age In eight of nine cases complicated by rheumatic involvement of the mitral valve pulmonary vascular lesions were greater than in controls and occurred earlier With superimposed mitral disease a mechanical factor is introduced which greatly

(9) Am J P th 24 729 761 J ly 1948

has also made workers conscious of the risk The editor has recently seen a patient whose pulmonary disease seems definitely related to the handling of fluorescent lighting tubes in a large theater His job was to dispose of old tubes which he did by breaking them into an ash can He was not aware of the cause of hi increasing disability until he heard a warning over the radio —Ed.]

Value of Beryllium Determinations in Diagnosis of Berylliosis F R Dutra J Cholak and D M Hubbard[8] (Univ of Cincinnati) used an accurate spectrographic method for determining minute quantities of beryllium in fluids or tissues of patients suspected of having berylliosis Analysis of 24 hour urine specimens of 27 perso suggested that most persons with acute beryllium pneumonitis may be expected to have small quantities of beryllium in the urine Beryllium was found at least once in urines of 5 of 14 patients with occupational chronic pulmonary berylliosis Excretion of the substance varies from day to day so that a few negative results do not rule out its presence

The toxic agent was present in 24 hour urine specimens of three of five patients with nonoccupational chronic pulmonary berylliosis None was found in the urine of six patients who had recovered from acute pneumonitis and were no longer working in the beryllium industry All of six patients who had recovered from acute pneumonitis and resumed work in the industry were excreting beryllium in the urine Healthy persons working in the industry also excreted beryllium

In a few subjects beryllium could not be recovered from the sputum but was detected in blood and renal calculi Tissues from 7 persons who died of acute pulmonary berylliosis and 9 of 10 persons dying of chronic disease contained varying amounts of beryllium In those who died there was no correlation between duration of exposure or illness and amounts of beryllium recovered from the lungs

Amounts of beryllium in urines of apparently healthy persons exposed to beryllium dusts were approximately the same as in persons with acute or chronic pulmonary

(8) Am J Cl P th 29 9 234 M ch 1949

teristic finding is ischemia of the involved pulmonary segment represented on an x ray by a segmental area of increased radiability whose shape is determined by configuration of the involved pulmonary segment Central to the embolism site the vascular pattern is well outlined *but in the area itself the vascular pattern stops rather* abruptly There are often increased density and sharper demarcation of the involved vessel The local area with diminished or absent vascularization corresponds to the pulmonary segment supplied by the occluded artery

Differential diagnosis includes obstructive emphysema and localized areas of nonobstructive emphysema In the former one sees a shift of the mediastinum toward the normal side and depression of the involved diaphragm during expiration Localized areas of nonobstructive emphysema may be more difficult to distinguish

Experimental Pulmonary Infarction Abnormal Pulmonary Circulation as Prerequisite for Pulmonary Infarction Following Embolus Don W Chapman Lloyd J Gugle and Paul W Wheeler[2] (Baylor Univ) produced pulmonary embolism in 12 normal mongrel dogs by releasing from the jugular veins blood clots produced by thrombin injections At autopsy 3 10 days later lung infarction was not demonstrable

Pulmonary congestion occurred in four dogs receiving alpha naphthylthiourea intravenously Of eight receiving alpha naphthylthiourea just before release of intravascular clots three showed pulmonary infarction distal to emboli and four showed intra alveolar hemorrhage without necrosis distal to the emboli

The results substantiate the observations of other investigators that embolism alone does not result in infarction of the normal lung This is probably because blood supplied by bronchial arteries or through anastomoses between intralobular pulmonary arteries is adequate to maintain nutrition Interference with this circulation by production of pulmonary congestion or edema or both is apparently a prerequisite for infarction following

( ) A h I t M d 83 158 163 F bru 1949

alters the existing dynamics of blood flow within the heart. Increased pulmonary blood flow is followed by development of widespread pulmonary vascular sclerosis.

There was no dilatation or gross evidence of atherosclerosis of the pulmonary arteries in 11 cases of significant unguarded interventricular septal defects. Microscopic evidence of intimal proliferative and hyaline changes in the pulmonary vessels was found in one case in which there was a 2 cm. interventricular septal defect, the largest in the series. In six patients with a combination of lesions giving a left to right shunt, the pulmonary atherosclerotic change was proportionate to the patient's age and the magnitude of the shunt. The question is raised whether modern surgical operations to relieve the symptoms of congenital pulmonic stenosis may not promote development of pulmonary atherosclerosis.

The common factor in cases with pulmonary vascular lesions was marked increase in pulmonary blood flow.

[Accelerated development of pulmonary atherosclerosis by such disturbances of circulation emphasizes the mechanical factors which may be implicated. It is seldom possible to diagnose these pulmonary vascular changes clinically, but the finding of pulmonary hypertension may suggest their presence.—Ed.]

Pulmonary Embolism without Infarction. Robert Shapiro and Leo G. Rigler[1] (Univ. of Minnesota) report three cases confirmed at autopsy of pulmonary embolism without infarction. Embolism of a lung in a person with normal circulation does not ordinarily produce infarction. In patients with cardiac decompensation infarction is rather frequent. This paradox is explained by dual circulation to the lungs through bronchial and pulmonary vessels. Westermark found that only 20 per cent of cases in which pulmonary embolism was established at autopsy showed evidence of infarction. He concluded that hemorrhagic infarction does not occur unless there is occlusion of both the bronchial and the pulmonary arteries.

In pulmonary embolism without infarction the charac

(1) Am. J. Roentg. 60: 460-465, Oct. 1948.

in the less severe forms of pulmonary embolism whereas in patients with fatal emboli debility and impaired general health were predisposing factors

Phlebothrombosis or thrombophlebitis was recognized clinically before fatal embolism in only seven cases Premonitory nonfatal pulmonary embolic attacks occurred in 14 whereas 42 had no warning infarcts before death

With phlebothrombosis interruption of the venous trunk above the site of thrombosis is indicated because anticoagulants though preventing further propagation of thrombus do not reduce the danger of embolism from a thrombus already present In thrombophlebitis anticoagulants should be used to prevent formation of a bland thrombus but ligation is not indicated since without it there is little risk of massive embolism

Treatment —As soon as thrombophlebitis develops 50 mg heparin is given intravenously every 4 hours for 48 hours Oral *administration of dicumarol*[®] *is started simultaneously* and consists of a single dose of 300 mg the first day 200 mg the second and 100 mg the third day From this time on dosage is regulated by daily determinations of prothrombin time Exercise and motion are encouraged and the patient i al lowed up with support of an elastic bandage as soon as temperature has become normal

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UNUSUAL CONDITIONS

Tumor Forming Amyloidosis of Lung Report of Case is presented by Allan L Haynes (Mayo Found) O Theron Clagett and John R McDonald[4] (Mayo Clinic) The most familiar manifestations of amyloidosis are extensive deposition of amyloid in liver kidneys and spleen in the course of chronic suppurative disease In recent years deposits of amyloid have been seen with increasing frequency in other organ with or without preceding disease Primary amyloidosis usually involves multiple sites in mesodermal tissues such as the heart

(4) S g y 24 1 01 4 J ly 1948

embolus to the lung This observation is substantiated by clinical and autopsy findings

[This and the following article complement each other The possibility of a roentgen diagnosis of pulmonary embolism without infarction is apparent from the work of Shapiro and Rigler although it may be very difficult The differentiation of segmental obstructive emphysema is particularly perplexing since there is no shift of the mediastinum during expiration but only the persistent illumination of the involved segment similar to that in embolism—Ed.]

Pulmonary Embolism Its Incidence, Significance and Relation to Antecedent Vein Disease Pulmonary emboli of some degree were found by Leo M Zimmerman Daniel Miller (Chicago) and Alfred N Marshall[3] (Portland Ore) in 6 1 per cent of 5 588 autopsies (representing an over all postmortem percentage of 56) The emboli were classed as purely incidental findings in 166 of which 154 originated in bland thrombi and only 12 from infective phlebitides There were 108 emboli from bland thrombi 5 from nonsuppurative thrombophlebitis and 10 from suppurative phlebitis which contributed partially to the patient s death Massive primary or fatal emboli resulted from bland thrombi in 53 instances and 3 occurred in patients with nonsuppurative thrombophlebitis but were probably also bland thrombi which developed as tail parts to thrombophlebitic processes Fatal emboli were found in 1 per cent of all autopsies a much lower incidence than is generally indicated

Incidental emboli arose mainly from small mural thrombi in auricular appendages in patients with cardiac decompensation or auricular fibrillation or from ventricular walls and sites of myocardial infarction Although many contributory emboli originated in the heart the most frequent site of origin was veins of the lower extremities Almost all fatal emboli arose from lower extremity veins Most incidental and contributory emboli occurred in medical patients but fatal emboli were three times more frequent in surgical patients Massive embolism was the primary cause of death in 0 05 per cent of patients undergoing major surgery

Cardiac disease was an important predisposing factor

(3) S g Gy & Ob t 88 373 388 M h 1949

lateral incision and resection of part of the sixth rib A hard mass with characteristics of malignancy was found the right lung was resected and the right phrenic nerve interrupted The stony hard mass 6 cm in diameter in the middle lobe (Fig 61) completely occluded the middle lobe bronchus Microscopic examination revealed deposition of amyloid in interalveolar septa particularly around blood vessel Alveoli were com pressed and confluent masses of amyloid compressed the bronchus No evidence of preceding suppurative disease was found

[Recently a patient in the Chest Service of Bellevue Hospital died pre umably of pulmonary failure secondary to atypical pul monary fibrosi At autopsy the condition wa found to be due t di seminated primary pulmonary amyloidosis an extremely rare occurrence —Ed]

Gumma of Lung Report of Case Treated by Lobectomy *is presented by Charles W Findlay Jr William L* Lehman and Louis A Rottenberg[5] (New York City)

Man 59 was hospitalized Oct 27 1947 because of pain in the left side of chest and persistent cough productive of small amounts of yellow nonfoul nonbloody sputum of five weeks duration Hi tory included penile lesion at age 18 with sub sequent positive Wassermann reaction and several injection treatments Dulness and tubular breathing with fine crackling respiratory rales were heard over the left lower lobe posteri orly Blood Kline and Wassermann test reactions were 4 plus to all antigens Colloidal gold curve was flat and spinal fluid Wassermann reaction negative Chest x ray (Figs 62 and 63) showed a well defined lobulated area of increased density po teriorly and medially in left hemithorax Penicillin 400 000 units daily intramuscularly for 12 day and subsequently when diagnosis of gumma of the lung was contemplated 1 000 000 units daily for 2 weeks resulted in progre sive de crea e in volume of the lower part of the left lung in which the le ion was thought to be with elevation of the left side of the diaphragm as seen on x ray A month after admission left lower lobectomy was carried out because of failure of medical treatment and the impossibility of ruling out neoplasm Gross and microscopic examination of the surgical specimen (Fig 64) confirmed the presence of a 7 × 7 × 4 cm gumma Post operative cour e was uneventful

Gumma of the lungs is twice as common in males as in females but the course in the latter is more fulminating Symptoms are those of any chronic low grade lung

(5) A g 1 9 74 284 F b y 1949

lungs and skeletal muscles Occasional large solitary masses of primary amyloid are found in these mesodermal tissues Tumor forming amyloidosis has been observed in the skin tongue larynx trachea urinary bladder and urethra

Man 60 was referred for treatment of a tumor of the right



Fig 61—Amyl d m s m dll lol of lu g d g d oc luding m ddl l be b h s n r it g Adj t t of m dll l be s d d ced l m (Co rt y f Ha n A L t l Su g ry 24 1 1 4 July 1948)

lung In addition he had thyrotoxicosis and was treated with iodine and thyroidectomy X ray revealed an obstructive lesion of the middle lobe bronchus and atelectasis of the lobe Bronchoscopy did not disclose a tumor and microscopic examination of secretions obtained from the bronchus did not reveal neoplastic cells Bronchography however showed a filling defect of the middle lobe bronchus

The right side of the thorax was exposed through a postero-

serologic reactions may be negative Pulmonary tuberculosis should be ruled out by repeated examinations of sputum concentrates or gastric washings for acid fast bacilli by competent technicians There are no characteristic x ray features of the disease and the more common diseases such as tuberculosis neoplasm and chronic pneumonitis should be excluded before pulmonary gumma is diagnosed

If the lesions do not respond immediately and strikingly to antisyphilitic drugs exploratory thoracotomy should be performed to make certain that the lesion is not carcinomatous If the lesion is a gumma and does not respond to medical treatment permanent and serious parenchymal de truction has probably occurred In such conditions the lung will be a site of repeated secondary pyogenic infections or may be a potential source of hemorrhage and should be removed by lobectomy or segmental lobectomy

[The rarity of gumma of the lung should be kept in mind when considering the diagnosis —Ed]

Diverticula of Thoracic Esophagus According to Herbert G Adams[6] (Lahey Clinic) traction diverticula usually occur in the midesophagus and are associated with inflammation of adjacent hilar nodes They are rarely large enough to obstruct the esophagus or to retain food and therefore surgery is rarely necessary unless there are complications such as periesophageal abscess or bronchial fistula Most diverticula of the pulsion type occur in the pharyngocervical esophagus Technical aspects of the surgical management of these diverticula have become well established Because pulsion diverticula of the thoracic esophagus are rare surgical technic is less well established

Symptoms from diverticula of the esophagus are related to progressive mechanical esophageal obstruction and range from indefinite gastric symptoms substernal distress and pain dysphagia regurgitation vomiting and finally malnutrition and debility

(6) J Th S g 17 639 645 Octob 1948



F g 62 (l ft) —Gumm of lung p t r t or v ew
F g 63 (ght) —Same lung l te al v ew
(Cou t sy f Findl C W Jr et l Ann Su g 129 274 84 Febr ary 1949)



F g 64 —Low r l be of left l ng h w g gr y rubb ry lobular ma s occupy g mo t of lobe and ach ng pleu Ba f l ng t left. (Cou t y of Findlay L W Jr et l A n S g 1 9 74 84 F bru y 194)

infection and physical findings are those of pulmonary consolidation The blood Wassermann test has diagnos tic value but if antisyphilitic therapy has been instituted

Though there may still be occasional indications for the operation performed on the first three patients Adams recommends that excision of the sac be carried out in most patients with e ophageal obstruction from diverticulum of the thoracic esophagus

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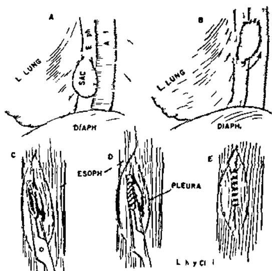
TRAUMA AND MECHANICAI INJURIES

Rupture of Bronchus Due to External Chest Trauma Report of Three Cases with Recovery Paul H Holinger (Chicago) Albert R Zoss (Cincinnati) and Kenneth C Johnston[7] (Chicago) state that rupture of a bronchus is an unusual and serious complication of severe external trauma The mechanism by which trauma produces bronchial rupture is unknown In recorded cases auto mobile injuries predominate No mention ot bronchial injury is made in surveys of chest injuries encountered in World War II The left bronchus is more frequently involved and the usual site of injury is just below the corvna If the individual survives the immediate injury some degree of bronchial stenosis usually complete inevitably results

Following bronchial injury the airway becomes per manently and completely interrupted aeration to the affected lung ceases and rapid absorption of trapped air with complete parenchymal collapse occurs The in volved lung remains in a chronic state of simple or un complicated atelectasis Negative intrapleural pressure on the affected side rises noticeably This is followed by shift of mediastinal structures contraction of the hemo thorax elevation of the diaphragm and distention of the contralateral lung Distention and possible emphysema are more serious in adults than in children Absence of infection in the chronically collapsed lung is striking and is probably due to lack of significant pre existing infec tion and to the barrier to subsequent bacterial invasion from above

(7) La y g p 58 817 833 A gu t 1948

Adams operated on five patients with pulsion diverticula of the thoracic esophagus Details of the technic are shown in Figure 65 *A* and *B* show the technic used in three patients before penicillin was available The apex of the sac was elevated along the long axis of the esophagus and sutured to the pleura at the highest point of elevation which would not produce traction or angulation



Fg 65 —Ope t v p oc d f t eatm t f th ac c d rt l *A* n l depe d t l t n t ph g *B* l t n d fi t f d t l p y *C* *D* l *E* p at atep n t g c f s c (C t y f A l H D J Th c Su g 17 639 645 O t l 1948)

of the esophagus This maneuver permits free drainage of the sac *C* *D* and *E* show the technic used in two patients given penicillin every three hours for two days before operation and continued after operation The sac was clamped and excised

All patients obtained complete and lasting relief from esophageal symptoms Of the first three patients two were asymptomatic for one year and five years until they died of miliary tuberculosis and coronary occlusion respectively one was well seven years after operation

days duration He had been unconscious 4 days after an auto mobile accident 4½ months previously Chest x ray taken 10 days after the accident revealed moderate interstitial emphy sema throughout the right lateral chest and in the right side of the neck fracture of the right first rib right pneumothorax with approximately 35 per cent collapse of right lung and elevation of right hemidiaphragm Dyspnea persisted after the accident but did not become severe until two days before rehospitalization

Physical examination revealed complete collapse of right lung with pronounced displacement of trachea and whistling breath sound on the right X rays verified previous findings and showed the right main stem bronchus to be occluded just beyond the carina Bronchoscopy failed to reveal a tumor at this area and lipiodol® injection showed bronchial occlusion complete 1 cm beyond origin of the right upper lobe bronchus Biopsy of the region revealed only bronchial tissue

Operation was performed No tumor could be palpated but the right lung was removed Pathologic study showed atelecta sis of the right lung with a cicatrix of the right main stem bronchus

Tears of main stem bronchi at or close to bifurcation of the trachea have been reported after severe chest in jury in 32 patients The usual clinical picture in these patients is shock dyspnea anoxia interstitial em physema and cough Persons who survive such accidents may develop post traumatic bronchial occlusion with pulmonary collapse Chest x rays may reveal rib frac tures interstitial emphysema pneumothorax pulmonary compressions and mediastinal shifts Where bronchial occlusion is complete classic x ray findings of pulmo nary collapse develop Bronchograms reveal cup shaped blind pouches at site of occlusion

Spontaneous Rupture of Esophagus Thomas J Kin sella Russell W Morse and Ambro e J Hertzog[9] (Min neapolis) found the condition reported in the literature more than 50 times Among these patients correct clini cal diagnosis was made only 14 times Death occurred in all but four in two of these esophageal rent was re paired surgically and in the other two empyema formed and healing occurred after esophageal fistulas had closed

(9) J Th S g 17 613 631 O t be 1948

Diagnosis of bronchial rupture immediately following the major injury is difficult because concomitant injuries usually complicate the picture No single or composite clinical findings are pathognomonic of bronchial injury at this stage Bronchoscopy is too hazardous and unwarranted in the early critical phase Presence of persistent lung collapse after survival is assured demands further study by bronchoscopy and bronchography When the patient is seen many months or years after injury diagnosis of a previous bronchial injury may not be simple Symptomatology is variable and not distinctive Chest x rays will show the total lung collapse and suggest the underlying bronchial obstruction which should be investigated appropriately

Immediate treatment of chest trauma complicated by bronchial rupture does not differ from that of any chest injury When the early critical phase has been survived and diagnosis established specific therapy should be seriously considered but because of limited possibilities for treatment none has been evolved Operative repair of the ruptured bronchus has been suggested but not attempted Patients in the late phase with no evidence of respiratory impairment probably require no active therapy Pulmonary resection offers the only prospect of complete cure for patients with partial stenosis when complicating bronchopulmonary infection develops In those with persistent respiratory symptoms and high negative intrapleural pressures on the involved side therapeutic pneumothorax should be instituted If symptom causes are not apparent trial of artificial pneumothorax is justified In adults thoracoplasty to correct mediastinal displacement and to limit overdistention of the contralateral lung may be considered if pneumothorax is not feasible

Traumatic Bronchial Rupture with Occlusion is described by Philip J Hodes Julian Johnson and Joseph P Atkins[8] (Univ of Pennsylvania)

Man 36 was hospitalized because of severe dyspnea of two

(8) Am J Roentgen 1 60 448 459 October 1945

days duration He had been unconscious 4 days after an auto mobile accident 4½ months previously Chest x ray taken 10 days after the accident revealed moderate interstitial emphy sema throughout the right lateral chest and in the right side of the neck fracture of the right first rib right pneumothorax with approximately 35 per cent collap e of right lung and elevation of right hemidiaphragm Dyspnea persisted after the accident but did not become severe until two days before rehospitalization

Physical examination revealed complete collapse of right lung with pronounced displacement of trachea and whistling breath sounds on the right X rays verified previous findings and showed the right main stem bronchus to be occluded just beyond the carina Bronchoscopy failed to reveal a tumor at this area and lipiodol® injection showed bronchial occlusion complete 1 cm beyond origin of the right upper lobe bronchus Biopsy of the region revealed only bronchial tissue

Op ration was performed No tumor could be palpated but the right lung was removed Pathologic study showed atelecta sis of the right lung with a cicatrix of the right main stem bronchus

Tears of main stem bronchi at or close to bifurcation of the trachea have been reported after severe chest in jury in 32 patients The usual clinical picture in these patients is shock dyspnea anoxia interstitial em physema and cough Persons who survive such accidents may develop post traumatic bronchial occlusion with pulmonary collapse Chest x rays may reveal rib frac ture interstitial emphysema pneumothorax pulmonary compressions and mediastinal shifts Where bronchial occlusion is complete classic x ray findings of pulmo nary collapse develop Bronchograms reveal cup shaped blind pouches at site of occlusion

Spontaneous Rupture of Esophagus Thomas J Kin sella Russell W Morse and Ambrose J Hertzog[9] (Min neapolis) found the condition reported in the literature more than 50 times Among these patients correct clini cal diagnosis was made only 14 times Death occurred in all but four in two of these esophageal rent was re paired surgically and in the other two empyema formed and healing occurred after esophageal fistulas had closed

(9) J Tb S g 17 613 631 Oct b 1948

The authors report five cases Correct diagnosis was made clinically in three patients and prompt surgical repair saved the life of one

CASE 5 — Man 67 had sudden onset of severe pain in epigastrium and left chest and immediately collapsed There was nothing in personal or family history to elucidate the episode He had marked respiratory distress and shock The left chest was hyperresonant and without breath sounds The abdomen was not tender or rigid and contained no masses On admission he was believed to have a spontaneous left pneumothorax Findings of subcutaneous emphysema and left hydropneumothorax suggested diagnosis of ruptured esophagus A small amount of barium given orally appeared promptly in the left pleural cavity

Operation was begun 8½ hours after onset of symptoms The chest was opened through a posterolateral incision with resection of a large segment of the ninth rib posteriorly A liter of food and fluid was removed from the pleural space and a 4 cm perforation of the left posterolateral esophageal wall just above *the cardiac end of the stomach* was repaired No ulceration or neoplasm was seen Four catheters were inserted through stab wounds in the left pleural cavity the chest was closed and penicillin and sulfadiazine were administered Fluid and blood were used postoperatively and continuous suction was maintained on intercostal catheters

A chest x ray five days after operation showed a density in right lung field interpreted as pneumonia On the eighth day he had sudden severe pain in the right chest a transient drop in blood pressure and was irrational There was no expectoration of blood Toward midnight he had another attack of chest pain and died six hours later Autopsy revealed the immediate cause of death was pulmonary embolism Source of emboli was not determined

The clinical picture in this condition is characteristic An apparently healthy person usually a man often addicted to eating and/or drinking heavily suddenly develops excruciating pain in epigastrium and left chest and shock Often the patient has just finished a large meal but some patients vomit because of a neurogenic lesion or some other reason Pain does not respond to large doses of morphine The most frequent misdiagnosis has been ruptured peptic ulcer but all other acute upper abdominal and chest complications may be con

sidered Physical findings in the chest suggest diagnosis Findings of diagnostic value by x ray include medi astinal emphysema a fluid level in the mediastinum pneumothorax on one or both sides (usually left) a fluid level in the pneumothorax and absence of subphrenic air (noted in only about three fourths of patients with gas tric or duodenal perforation) Aspiration of fluid resem bling vomitus from the pleural cavity aids diagnosis

Hertzog inflated the stomach and esopha us of ca davers and found that pressure necessary to burst the stomach was 4 9 mm Hg and the esophagus 10 33 mm Hg Healthy young adults can easily blow pressures of 110 190 mm Hg

Spontaneous Rupture of Esophagus Report of One Case with Recovery is made by Julian A Moore and James D Murphy[1] (Veterans Hosp Oteen N C)

Man 33 was admitted to a civilian hospital becau e of sud den sever left epigastric pain and vomiting of blood the morning after he had consumed five highballs For 10 years he had had indigestion which had been attributed to p ptic ulcer without radiographic verification After one previous similar attack he had been op rated on and was told that he had acute pancreatiti

Operation was performed 5½ hours after hospitalization on the presumption that he had a perforated peptic ulcer but careful search of the peritoneal cavity revealed no cause for his symptoms Six day after operation a chest x ray rev al d widening of the mediastinum and left hy lropneumothorax Thoracentesis yield d 135 cc of clear amber fluid without organisms After many thoracenteses purulent pleural fluid sour smelling and acid in reaction was found Barium given orally appeared in the left chest Diaphragmatic hernia with perforated ulcer in the herniated portion of the tomach was diagnosed

The patient was tran ferred to the Veterans Administration Hospital and a left thoracotomy was p rformed for drainage of empyema Jejunostomy was also performed improving nutrition o that 22 day later it was fea ible to repair the suppo ed diaphragmatic hernia

When the chest was entered the tomach was not found but examination of the esophagus revealed a 4 cm rent just above

(1) J Th S g 17 63 638 O t b 1948

the diaphragm which was repaired Penicillin was continued through an uneventful convalescence and the patient was discharged four months after operation completely well

The authors favor waiting to repair spontaneous esophageal ruptures because of the precarious condition of patients immediately after such catastrophes and the tendency of the lesions to heal spontaneously They recommend immediate drainage of the thoracic cavity use of antibiotics and maintenance of nutrition by jejunostomy

THE BLOOD *and* BLOOD-FORMING ORGANS *and* THE KIDNEY

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(Edinburgh and London)

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M D (Hon) Utrecht

PART III

THE BLOOD AND BLOOD FORMING ORGANS AND THE KIDNEY

GENERAL CONSIDERATIONS

The articles in this section consider some general principles that concern the functions of the blood and blood forming organs in normal and pathologic conditions —Ed

Oxygen Saturation in Bone Marrow and in Arterial and Venous Blood during Prolonged Hemorrhagic Erythropoiesis was studied by Wilson C Grant[1] (Columbia Univ) Anemia was induced in eight male dogs by repeated small hemorrhages and this condition was maintained for 40 100 days Diet was adequate and contained 50 60 mg total iron but was not supplemented with hematinic substances Hemoglobin concentration of jugular vein blood was maintained at 48 71 per cent of normal during the study Oxygen saturation of arterial jugular venous and bone marrow blood was measured once or twice before anemia was produced and thereafter that of bone and venous blood at approximately weekly intervals and that of arterial blood less frequently

Reticulocytosis between 2 and 5 per cent during the anemic period indicated that active red blood cell regeneration was in progress Grant s calculations indicate that red blood cell regeneration was proceeding so rapidly that the mass of erythrocytes produced in one week equaled 38 per cent of total volume of bone marrow

Arterial oxygen saturation was unaffected by the hemorrhagic anemia Oxygen saturation of marrow and jugular vein blood showed great individual variation in anemic and in nonanemic animals Oxygen saturation of marrow blood was not significantly different during

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(1) Am J Phy 1 153 5 1 5 8 J 1948

iron intake must determine size of body iron stores Dietary iron requirements have been set at about 12 mg daily though the actual requirement for iron is probably less than 1 mg daily The discrepancy is explained by the fact that of the 12 mg in diet less than 10 per cent is absorbed in normal man However iron absorption is more efficient in the presence of iron deficiency and may increase to 50 per cent or more Absorbed iron is distributed through the body via plasma

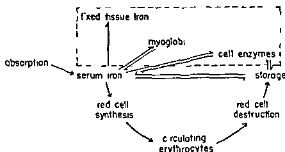


Fig 66—Diag m f on m tab l m Hem gl b y l h w ota t f n th gh bu m ow (ed ll y th) n blood t m ci l t g r d ll nd d tru t on f th ll d t rag f th n fe t d b m d w th t l t f n to rum on pool d bo m w W th n ta gl e l d d t on f t t d w h h m gl b n y l Fix d t s o d gnated by H h p t th t f t f on wh h doe t ppe t b u ble f h mogl b n p od t d wh h tract d f m t w th d fficulty (C te y f F h C A Am I t 3 165 168 N mb 1948)

Plasma iron is bound to a B_1 globulin called the iron or metal binding protein Normally this protein is only 33 per cent saturated with iron and in iron deficiency saturation is below 10 per cent

About 75 per cent of total body iron is concerned with the hemoglobin cycle (Fig 66) Red cell destruction occurs in the reticuloendothelial system by phagocytosis of old cells or if cells are broken down intravascularly hemoglobin may be handled by the kidney In both instances however iron is returned for reuse by the bone marrow Thus body iron constantly rotates through the

anemia and control periods Oxygen concentration of jugular vein blood fell slightly during anemia Arterio venous and arteriomarrow oxygen difference decreased in anemia

Though striking and prolonged stimulation of erythro poiesis was produced in these animals there was no evidence to suggest lowering of the oxygen saturation of the marrow blood classically considered to be the stimu lus to erythropoiesis after hemorrhage

[Studies of the oxygen saturation of blood removed by sternal puncture from nonanemic and anemic patients as well as from some patients with polycythemia vera have likewise shown in our hands no consistent relative anoxia in the last two groups However as the technic used probably produces a sample of mixed ar terial and venous blood the results do not justify the abandonment of the hypothesis that hemoglobin production is usually regulated by the hemoglobin concentration of the peripheral blood for which so much indirect experimental and clinical evidence exists —Eds]

Pathologic Physiology of Hemoglobin Formation is discussed by Clement A Finch (Harvard Univ) The hallmark of anemias in which hemoglobin synthesis is primarily impaired is microcytosis and a reduced con centration of hemoglobin within the erythrocyte Hemo globin is produced in the normoblast and reticulocyte stage of erythrogenesis The period of hemoglobinization of the red cell is about four to six days and during this time a single developing red cell synthesizes some 300 000 000 hemoglobin molecules Though little is known of the process of hemoglobin synthesis certain facts are known of the metabolism of the three ingredi ents which constitute the hemoglobin molecule that is protoporphyrin globin and iron Protoporphyrin and globin are both synthesized in the body with ease and the possibility of their limiting hemoglobin synthesis is slight But the body frequently has difficulty in mobiliz ing sufficient iron for hemoglobin production In man iron deficiency is the most frequent cause of anemia

Figure 66 is a diagram of iron metabolism Iron is not actively excreted from the body only traces appear ing in urine and stools With no regulation of excretion

(2) Am P ct 3 165 168 N v mbe 1948

later become denucleated This assumption leaves several questions unanswered particularly the question of what becomes of all the nuclei Lisa Bostrom[3] (Stockholm) presents the hypothesis suggested by observations on circulating blood that red blood corpuscles are formed by the budding off of hemoglobin holding cytoplasm from the erythroblasts in the marrow not by denucleation The stalklike processes on the edge of the erythrocyte disk seen so often in poikilocytosis are assumed to be real stalks by which erythrocytes were once attached to the capillary wall (Fig 67) Thus stalkless blood cor

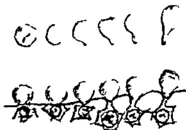


Fig 67—S h ma p se t f w ll f m d ll y h w g f mat on ot a g po k locyt (Court y f L t uem L A ta m L S d (31 3)3 3 4 1948)

puscles would be formed when the capillary wall is extremely thin as in normal circumstances A thickened wall or an abnormally long distance between the mother cell outside the vessel and the erythrocyte inside the vessel would require a bridge between them Adherence of this link to the cell when it i detached would explain the stalklike process of the poikilocyte The process would thus be a malformation which reveal something of the mechanism of erythropoiesis Then one erythroblast could form several erythrocytes by the simple process of budding off additional cytoplasm

This hypothesis is supported by a number of facts Erythroblasts of the marrow are not sufficient for the

(3) Acta med S d 131 303 3 4 1948

hemoglobin cycle Smaller amounts of iron are concerned with cell enzymes and myoglobin

Two protective devices guard against development of iron deficiency anemia (1) tissue stores which contain iron immediately available to supplant that lost from the body and (2) ability to increase iron absorption Adequacy of body iron stores may be estimated by sternal aspiration In marrow fragments hemosiderin in small amounts is normally seen in the reticuloendothelial system but it is absent in iron deficiency This is a useful guide to iron therapy particularly in differentiation of iron deficiency anemia from anemia of infection

Adequate treatment of iron deficiency consists of 0 2 Gm ferrous sulfate after each meal except when larger amounts are needed to balance blood loss Blood picture usually reverts to normal within a month If more rapid treatment is desirable blood transfusion will supply 2 0 mg iron already contained in erythrocytes more satisfactorily than any other injectable form of iron

Iron metabolism is abnormal in infection Although excessive iron deposits are present in tissues there is a relative iron deficiency in serum and red cells This appears to be due to increased affinity of tissues for iron in infection and a general bone marrow depression Iron therapy by mouth or parenterally is of no value in anemia of infection since the iron is merely deposited in tissue stores The only effective therapy other than that directed at the specific infection is blood transfusion

[Cobalt administration in experimental animals and in man will elevate the moderately depressed hemoglobin values associated with chronic infections It is questionable however whether this is a useful procedure especially since the possible toxic effects of cobalt have not been fully explored —Eds]

Are Non Nucleated Erythrocytes Formed by Budding Off of Cytoplasm from Normoblasts? Based on demonstration of the presence of nucleated red blood corpuscles in bone marrow is the assumption that non nucleated erythrocytes of the blood are formed from these elements and therefore that blood corpuscles develop from proerythroblasts into acidophilic normoblasts which

is a strong indication that the proerythrocytes are detached from cytoplasm of polychromatic normoblasts This budding off of protoplasm from normoblasts is a common observation in intense erythropoiesis Presence in bone marrow of normoblasts with giant cytoplasm is evidence that a normoblast is able to form more than one blood corpuscle

[By heating adult red cells it is possible to produce budding without loss of significant amounts of hemoglobin

The following article makes the very important point that a laboratory d termination often inaccurate should not be used without judgment Today all too often laboratory studies are sub tituted by busy physicians for a good talk with the patient and some reflection thereafter on the findings as a whole On the other hand because of the difficulty of helping the many patients with potentially fatal forms of blood dyscrasia no specialist in this field will regret the opportunity to help demonstrate that the trouble is something else and remediable

We should like at this point to mention the lack of wisdom of the physician who suspecting the presence of leukemia makes his patient aware of this circumstance before it is necessary to do so The undoubted value of the current education of the public with regard to the early recognition of *locali ed* cancer finds no parallel advantage in the case of a generalized and incurable disease such as leukemia Indeed in some of the more chronic forms of leukemia it is unwise to initiate therapy until symptoms appear Certainly there is no need for the patient to learn from a careless word the nature of his illness Until the great day arrives when there is a cure may we remind physicians that today the express on too many white cells or someth ng wrong with the blood may have d re impl cations for the cancer minded modern American that it never before possessed —Eds]

Red Cell and Hemoglobin Standards Use in Clinical Practice Clark W Heath[4] (Boston City Hosp) emphasizes the frequency with which hematologists encounter patients under treatment for anemia who actually have no anemia In a group of college girls the taking of iron for anemia when no deficiency was present was common equally prevalent were misconceptions concerning thyroid dysfunction and low blood pressure Gastrointestinal distress from oral administration of iron seems to occur more frequently in patients who do not have anemia than in those who do

Convincing patients that they do not have anemia and

(4) Ch g M Soc B ll 51 55 554 J 29 1949

enormous amount of erythrocytes required each day (about 25×10^{10}) if as in the denucleation theories one erythroblast can only form one erythrocyte Figures tally better if each erythroblast is assumed to form several erythrocytes The denucleation theory also cannot explain what becomes of all the extruded nuclei and no support for the concept of karyorrhexis and karyolysis is found in normal marrow The budding hypothesis explains why only normal sized nuclei if any are found in marrow If it is only a question of budding off of a piece of protoplasm, the mother cell would be left intact and no disintegration of nuclei would be necessary Eccentrically situated nuclei and detachment figures may be phenomena which occur while the cytoplasm is in the process of budding and detachment

The question of the way in which erythrocytes pass from the parenchyma of bone marrow into circulating blood is solved by the budding hypothesis even though the vascular system is presumed to be closed The controversy on whether erythropoiesis takes place within or outside the blood vessels is also settled The budding hypothesis shows that both are right for it assumes that the first phase of erythropoiesis takes place extravascularly and the second phase intravascularly

If it is assumed that erythrocytes are formed by budding off from erythroblasts then anisocytosis is readily explained as due to detachment of different sized pieces of protoplasm Reticulocytes fit nicely into the budding hypothesis The mature disk shaped erythrocyte cannot pass through capillary walls but the reticulocyte with its nonspecific more or less spherical shape can it is in this form that passage through the capillary wall takes place Since the name reticulocyte suggests reticuloendothelium the term proerythrocyte is preferred for this cell Another supporting fact is that the cytoplasm of the most mature erythroblasts of normal marrow the polychromatic normoblasts has exactly the same appearance as the cytoplasm of the blood s most immature erythrocytes the reticulocytes or proerythrocytes This

per cent [1] Hemoglobin level is an individual matter and similar ranges of normal are encountered wherever biologic material is measured

Concern with the immediate and remote biologic effects of radiation is a subject of vital importance to our civilization in peace and in war Devices or substances capable of producing energy of this type are now and will be used with increasing frequency The avoidance of hazard to those engaged in their handling and the effectiveness of treatment in the event of undue exposure demand full knowledge from a practical standpoint alone to say nothing of the desirability of such knowledge when irradiation is used for experimental purposes in animals or for therapeutic purposes in man The next two articles discuss the effects of radiation on the blood forming organs —Eds

Effects of Radiation on Hemopoiesis John S Lawrence Andrew H Dowdy and William N Valentine[5] (Univ of Rochester) point out that much confusion will be avoided in considering radiation effects on hemopoiesis if the following facts are recognized (1) Peripheral blood cells are relatively resistant to radiation and are directly affected only by tremendous amounts (2) The peripheral blood picture produced by radiation is greatly affected at any one period after irradiation by length of life of the different morphologic elements in peripheral blood Evidence now available indicates that white blood cells have the shortest life span platelets a somewhat longer span and red blood cells the longest Changes in these elements after radiation are therefore expected to occur first in white cells and last in red cells (3) The effect of radiation on the peripheral blood picture is influenced by radiosensitivity of the parent cells Since parent cells of lymphocytes are more radiosensitive than those of other blood elements radiation effect is expected to be greatest on lymphocytes (4) Ability of tissue to regenerate is of great importance

Most observations on effects of roentgen radiation applied to the whole body in a single dose have been made in animals In the rat after exposure to 500 r lymphocytes diminish precipitously the first definite diminution being noted 15 minutes after radiation and almost all

(5) R l) gy 51 400 413 S p mbe 1948

seeking other causes for their symptoms—often in the field of social adjustment—requires that the hematologist also be a good clinician Mistaken diagnoses of anemia may result from faulty technic in collection of blood faulty instruments used in determination of red cell counts and hemoglobin percentages or faulty interpretation of standards Failure to prick the finger deeply will on squeezing the finger dilute the blood with serum To avoid this error blood should be withdrawn from a vein Accurate technics and available standardizations must be relied on for performing accurate blood tests A certification of standardization of hemoglobin apparatus such as that for counting chambers and pipets is a definite need

In a study of 258 students at Harvard normal hemoglobin concentrations ranged from 12 6 to 16 8 Gm with the great majority between 14.2 and 16 1 Though average hemoglobin was 15 2 Gm range of normal was so great that use of percentages had little meaning Wide variation in other physiologic functions was also found normal oral temperatures ranging from 96 5 to 100 2 F Emotional strain often produced polycythemia and in such persons there was usually concomitant tachycardia

Average hemoglobin values at birth approach 20 Gm / 100 cc During the first few weeks of life this figure falls to about 12 Gm and for the first five years remains at about 12 5 Gm Then there is a gradual rise to adult figures which approximate 15 Gm for men and 13 5 14 Gm for women In old age the average falls 12 7 Gm for men and 11 7 Gm for women were found in institutionalized persons In pregnancy a reduction of hemoglobin levels to 11 12 5 Gm is normal To express hemoglobin values in terms of percentages of normal is therefore a misconception To adopt a figure for 100 per cent hemoglobin is unnecessary if hemoglobin is referred to only in terms of grams per 100 cc It is rather strange that hemoglobin ever was described in terms of percentages It would be strange indeed if physicians referred to someone s height as 80 per cent and w ... ht as 1 0

dosage levels of radiation vary chiefly in a quantitative manner Bryan and Sutter and their co workers found that with 550 r radiation injury was apparent one hour after irradiation At six hours cytolysis of cells in lymph follicles had reached its maximum and at 24 hours regeneration and repair of lymph nodes was actively progressing Regeneration in lymph nodes was complete 21 days after irradiation but number of lymphocytes in peripheral blood was still below normal 25 days after irradiation Similar changes were observed in the spleen though the whole process was more prolonged regeneration not being complete until 40 days after exposure Cellular destruction in bone marrow was maximal 2½ 5 hours after irradiation and regeneration was complete after 40 days Figure 68 shows the time at which regeneration began in the various cellular elements in peripheral blood

Results of experimental studies of the effect of repeated small doses of whole body irradiation are less definite In all species of animals studied daily exposure to 10 r per day resulted in detectable change in some hemopoietic elements within a year Despite the fact that with smaller doses of radiation it was not always possible to detect hemopoietic change no radiation dosage given was so small that mean survival time of large groups of animals was not affected Thus total dosage is of great importance and within limits the effect of roentgen radiation given in small daily increments is cumulative Incidence of leukemia was definitely increased in animal groups subject to chronic irradiation

Animal experiments indicate clearly that local irradiation of a portion of the body produces no effect on hemopoietic tissue not directly in the exposed area

Since most human exposure to radiation is to small repeated doses the most important conclusions from experimental studies are the observation relating to cumulative effect of small doses and the importance of the total amount of radiation to which an individual has been exposed Furthermore the possibility of leukemia

lymphocytes being absent 12 hours after radiation Line of descent parallels that of rate of utilization or life span of lymphocytes Granulocytes begin to diminish at 24 36 hours after irradiation platelets at 72 120 hours and red blood cells at 120 168 hours From these points on lines of descent closely approximate lines showing rates of utilization of the various cells It is readily seen

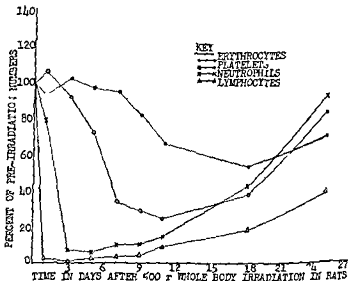


Fig 68—T me of d p s on d r g at n of the va io s c ll la ele m ts n pe ph l bl od f at r ce g 500 r whol body i r d t on (Data of S t r a d a s t s) (C t sy f Law e J S t al Radi ology 51 400 413 S pt mb r 1948)

therefore that rate of disappearance of the various elements is determined to a large extent by their rates of utilization or their life span

With doses of 200 r or less no significant alteration of red blood cells or platelets have been observed With doses less than 100 r reticulocytes are almost unaffected Doses of 25 r cause a drop in lymphocyte level in 24 hours

Morphologic changes in blood cells of rats at different

tion of these bodies requires a flawless supravital technic not widely available All these criteria represent abnormalities arising from depressed hemopoiesis increased lability of hemopoietic organs or abnormal maturation

Diagnosis of repeated small exposures may be facilitated by differential counts of radiation in urine feces and nasal secretions and by elimination of other potential industrial hazards Determination of repeated exposure to small amounts of ionizing radiation in groups of personnel may be carried out with somewhat more certainty by comparing average leukocyte counts of such groups with those of comparable control groups not subjected to any known toxic agent

Since most signs and symptoms appear relatively late after radiation injury protection must include physical control of radiation intensity by monitoring procedures and prevention of contamination of personnel by radioactive materials

Effect of Endocrinopathies on Blood William H Daughaday Robert H Williams and Geneva A Daland (Harvard Univ) present evidence from the literature and their own experience demonstrating that blood formation is influenced by the hormones of the gonads thyroid adrenal cortex and pituitary glands

The relatively low red cell count in women as compared with men cannot be attributed to menstrual blood loss becau e it is found in lower animals which do not menstruate Ovariectomy in rats causes a rise in red cell count and hemoglobin to nearly the levels maintained by castrated males which in turn are slightly lower than those in males before castration

Hypothyroidism results in moderately severe anemia In the uncomplicated form this anemia is slightly macrocytic and is associated with a hypoplastic bone marrow Clinically the anemia may be complicated by secondary effects of achylia gastrica leading either to iron deficiency or to deficiency in the anti pernicious anemia factor Hyperthyroidism is reported to cause leukopenia with

(7) Plood 3 134 1364 Dec mb 1948

must be considered whenever there is exposure to any appreciable amount of radiation

Ionizing Radiation Injury Its Diagnosis by Physical Examination and Clinical Laboratory Procedures is surveyed by Eugene P Cronkite[6] (Naval Med Research Inst) Diagnosis of a single excessive exposure to ionizing radiation by blood examination is not difficult Total body exposure to more than 25 r delivered within a few hours may be considered to constitute a single intense exposure The degree of lymphocytopenia will determine the severity of exposure It is possible that amounts less than 25 r may produce deleterious late effects

Early detection of excessive cumulative exposures is much more difficult and uncertain Penetrating radiation may cause generalized systemic and hematologic disorders in addition to the superficial effects of radiation with a low degree of penetrability Superficial lesions are limited largely to skin and eyes although an increased brittleness of finger nails loss of integrity of fingerprints and impairment of sensation in finger tips may occur Alteration in the blood however provides the most reliable criterion of chronic total body overexposure

Evidence of excessive exposure may be presumed to be present in a person with (1) white cell count persistently below 4 000/cu mm or (2) above 15 000/cu mm with absolute lymphocytosis (3) relative lymphocytosis with a total white cell count between 4 000 and 6 000/cu mm which returns to normal after removal from exposure (4) increased mean corpuscular volume shift in Price Jones curve to the right increase in mean corpuscular diameter (5) reticulocyte count over 2 per cent (6) red cell count over 5 800 000 or hemoglobin over 18 Gm/100 cc Though changes in blood coagulation prothrombin time and platelets and morphologic changes in leukocytes have been described they are difficult to evaluate at present The presence of refractile neutral red bodies in lymphocytes constitutes specific evidence of exposure to radiation or industrial poison but detec

(6) J A M A 139 366 369 F[illegible]

tion of these bodies requires a flawless supravital technic not widely available All these criteria represent abnormalities arising from depressed hemopoiesis increased liability of hemopoietic organs or abnormal maturation

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[7] [illegible] 1364 December 1948

reduction in polymorphonuclear neutrophils relative and absolute increase in lymphocytes and moderate increase in eosinophils but red cell count is not affected

Hyperactivity of the adrenal cortex is associated with polycythemia Administration of adrenocorticotrophic hormone or adrenal cortex extracts causes increase in polymorphonuclear neutrophils and decrease in lymphocytes and eosinophils Addison s disease is associated with relative increase in lymphocytes Lymphocyte destruction following administration of adrenal cortex extracts is accompanied by release of serum beta and gamma globulins Coincident with this rise in serum globulins the authors have observed an increase in agglutination titers

Hypofunction of the anterior pituitary results in an anemia which is usually microcytic and hypochromic and is associated with aplasia of bone marrow The authors have found that a combination of desiccated thyroid desoxycorticosterone acetate and testosterone provides a reasonably satisfactory method of treatment for hypopituitarism

Phagocytic Activities of Various Types of Leukocytes It has been found that monocytes and all polynuclear leukocytes except eosinophils have phagocytic activity but that lymphocytes and eosinophils do not phagocytize M Jersild[8] (Copenhagen) undertook to determine the phagocytic ability of immature leukocytes not normally found in peripheral blood

TECHNIC —Two cc of patient s blood defibrinated by vigorous shaking is added to a suspension of Brucella abortus and the mixture incubated at 37 C for half an hour A drop of the mixture is smeared on a slide washed and stained for 10 minutes with 0 2 per cent aqueous methylene blue which stains bacteria but not cytoplasmic granules Such slides observed through an oil immersion lens usually show 40 or more bacteria in a polymorphonuclear leukocyte

Studies of blood cells from normal bone marrow and from peripheral blood of patients with leukemia showed that myeloid cells younger than metamyelocytes are

(8) Acta med S d n (pp 213) 131 38

rarely phagocytic Lymphocytes and their precursors were not phagocytic Mononuclear cells from two patients with nonleukemic myeloid splenomegaly displayed active phagocytosis even when peroxidase negative a fact suggesting that the cells in this disease may be differentiated by their ability to phagocytize and shown to differ genetically from cells in lymphatic or myeloid leukemia

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METHODS

Articles in which technics used in d agnosis and treatment are the primary interest are included in this section —Eds

Aspiration of Bone Marrow from Iliac Crest Comparison of Iliac Crest and Sternal Bone Marrow Studies Michael A Rubenstein[9] (New York City) has performed over 1 000 marrow aspirations from the crest of the iliac bone since 1943 when he first attempted this procedure in a patient with carcinoma of the breast and x ray evidence of metastases in iliac bone Aspiration from the iliac crest proved so easy that he instituted this method as a routine procedure

TECHNIC—Puncture site is the crest of ilium within 5 cm immediately posterior to the anterior superior spine on either side of the body The needle similar to that usually used for sternal aspirations is 16 gauge 1 2/3 in long A 20 cc syringe is used The area is prepared with iodine and alcohol and infiltrated with 2 per cent procaine hydrochloride to the periosteum The patient is usually supine but is turned on his side if there is marked abdominal distention The needle is directed in the sagittal plane of the body at a 45 degree angle to the line of the crest When needle strikes bone it is changed to the perpendicular plane and directed over the top of the crest downward so that it is not aimed into the abdominal cavity The needle is forced into bone with steady pressure and slight rotation Distinct give is felt when needle enters medullary cavity Stilet is withdrawn and syringe attached to needle Smears are made in the usual manner

This method has several advantages over the customary sternal marrow aspiration technic It is safer and

(9) J A M A 137 1281 1285 A g 7 1948

less frightening and can be performed at frequent intervals if necessary The ilium might be utilized for administration of fluids into the general circulation when veins are inaccessible

Bone marrow aspirations from both sternum and iliac crest in 216 patients showed that normal and in most instances pathologic cell distribution is the same in the two regions Rubenstein recommends combined studies of sternal and iliac bone marrow in patients with patchy bone marrow disease

Multiple Sites for Bone Marrow Puncture, with Particular Reference to Children. Examination of bone marrow in hematologic disorders by means of puncture aspiration is an integral part of hematologic study and is often invaluable in diagnosis Although the sternum is the usual site for puncture alternate sites are often desirable Observations in adults indicated that essentially similar material is obtained from various sites punctured simultaneously Using the same technics in infants and children Jack J Rheingold Louis Weisfuse and William Dameshek[1] (Tufts College) found iliac crest and vertebral punctures of special value In infants particularly the sternal marrow cavity is quite shallow and possibility of perforation into the mediastinum is always present Furthermore spinous process puncture is often preferable for psychic reasons since the child [or adult—Eds] cannot see the activities associated with the procedure and consequently becomes less alarmed

TECHNIC—The same type of stiletted needle is used for iliac crest and spinous process punctures as is used for sternal approach For iliac crest puncture a small area just below the iliac crest is cleansed and skin subcutaneous tissues and periosteum are infiltrated with procaine hydrochloride The bone marrow needle is then pushed into the ilium distal to the crest (Fig 69) There is usually a distinct sense of give at which time the stilet is removed a 10 cc dry syringe is attached and a small amount of marrow aspirated Smears are made directly on specially cleaned glass slides

Spinous process puncture is performed with the patient lying face downward [or on the side—Ed] Lower thoracic

(1) New Engl J Med

and lumbar vertebrae are most satisfactory The spinous process to be utilized is grasped on either side with thumb and forefinger of the left hand and after infiltrating with procaine the bone *marrow needle* is introduced perpendicularly to the process After the sense of give is felt aspiration is performed

In adults bone marrow punctures using multiple sites were performed in 31 patients 3 of whom had sternal iliac crest and spinous process punctures Surprisingly similar findings were obtained both in eneral appear

Fig 69—Il t p ta b w g pos t th tb g k dl t m t f p ct (Court y f Rh g ld J J t l N w E gl d J M d 240 54 56 J n 13 1949)

ance of the marrow on microscopic study and in differential counts Occasionally marrow was obtained from one site when another yielded a dry tap Of 13 children who had punctures at multiple sites comparable results were obtained in 10 In the other three sternal puncture yielded no marrow or very dilute marrow and accurate diagnosis was possible only by iliac or spinous puncture

[In adults at least the iliac crest is the favored site for puncture in our hands Stern l pun ture s no longer performed—Eds]

Use of Preserved Erythrocytes for Detection and Identification of Rh Antibodies Because of the necessity of storing different Rh types of O erythrocytes for

blood testing at blood typing centers Paul G Hattersley and Margarette L Fawcett (San Francisco) determined titers of different type bloods stored in Alsever s or acid citrate dextrose (a c d) solution in a refrigerator for varying periods

TECHNIC—A donor group A MN Rh rh (cDE/cde) was bled and 5 cc blood mixed in each of a series of capped bottles with 5 cc sterile Alsever s solution One bottle was withheld for immediate study and the remainder stored at 4 C At weekly intervals one bottle was removed from the refrigerator for study and discarded Each specimen was titrated against a standard anti D (Rh_0) blocking serum of proved keeping qualities in the following manner (1) an approximately 2 3 per cent cell suspension was made in 30 per cent bovine albumin by adding 2 or 3 drops of the blood anticoagulant mixture to 1 cc albumin (2) standard anti D (Rh_0) serum was serially diluted in normal AB serum and 1 drop of each dilution placed in a series of small agglutination tubes (3) to each tube was added 1 drop of the cell suspension (4) all tubes were incubated in a 37 C water bath centrifuged three minutes at moderate speed and examined under the dissecting microscope for agglutination which was recorded as 1-4 plus

Titer fluctuated little that little probably being due to variations in technic until the seventh week Stored blood first showed gross hemolysis at this time In the two years that Alsever s and a c d solutions have been used in the authors laboratory there has been no evidence that cells preserved in this way are not perfectly reliable for Rh testing as long as there is no gross hemolysis

Sulfhydryl Compounds and Sickling Phenomenon Preliminary Report Lewis Thomas and Chandler A Stetson Jr[3] (Johns Hopkins Univ) studied the effect of a variety of reducing agents on sickle cells in order to devise a dependable method for rapid diagnosis of sickle cell disease They found that sulfhydryl compounds notably hydrogen sulfide BAL and cysteine caused complete sickling in less than a half hour in patients with sickle cell disease Glutathione and sodium chloride did not produce rapid sickling None of the thiol

(2) J Lab & Cl Med 33 1177 1179 S pt mbe 1948
(3) B ll J h Hopk s H p 83 176 180 A g 48

reagents produced sickling or any other change in contour resembling sickling in normal red cells Concentrations of each substance which produced sickling were also those which gave a positive nitroprusside reaction

Blood from three adult Negroes with the sickling trait but no history of the disease showed the same response to thiol compounds as blood from patients with the active disease but in two other adults with the sickling trait sickling occurred only after two hours exposure to hydrogen sulfide or BAL

It is postulated that thiol reagents block an SH mechanism within the cell but the effect may be due to some other less specific chemical trauma to the cell

Since hydrogen sulfide solutions maintain activity for five days when kept in tightly stoppered containers in a refrigerator whereas BAL and cysteine must be prepared in fresh solution every day and kept cold at all times the authors recommend use of hydrogen sulfide solutions to precipitate sickling When a drop of saturated solution of hydrogen sulfide is mixed on a slide with a drop of blood sickling of most of the cells is evident within 15 minutes in patients with sickle cell disease

[The use of sodium bisulfite solut on in similar fast on is perhaps more convenient and is described in the following article —Eds]

Simple and Rapid Method for Demonstrating Sickling of Red Blood Cells Use of Reducing Agents is described by Geneva A Daland and William B Castle[4] (Harvard Univ) Because sickle cell anemia is often misdiagnosed development of a simple method of detecting sickling phenomena is of practical importance Sickling appears when oxygen tension in the gas phase with which the blood is in equilibrium is 40 45 mm Hg or less Below this value oxygen tension which causes sickling depends on whether the active disease or only the so called trait is present Diminution in pH within the physiologic range increases tendency to sickling at a given oxygen tension because of the resulting greater percentage of reduced hemoglobin in red cells Thrombotic and hemolytic

(4) J Lab & Cl M d 33 108 1088 S ptembe 1948

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(2) J Lab & Clin Med 33 1177 1179 September 1948
(3) Bull Johns Hopkins Hosp 83 1 6 180 August 1948

of the types of increased red cell destruction However the first article which should be studied in the original presents as good a recent delineation of the probl m as exists in print.—Eds

Hemolytic Anemias Recent Advances in Diagnosis and Treatment Robert S Evans and Rose Duane (Stanford Univ) review recent work which elucidates the pathogenesis of hemolytic anemias and permits more efficient treatment of these disorders The classification which follows shows that hemolytic anemias may re sult from inherited abnormalities of red blood cells them selves or from acquired abnormalities of the blood chiefly antigenic or toxic in nature which stimulate red blood cell destruction

Classification of Hemolytic Anemias

A Hemolytic anemia due to cell abnormal ty
  1 Congenital hemolytic jaundice
  2 Sickle cell anemia
  3 Paroxysmal nocturnal hemoglobinuria (hemoglobinem a)
  4 Mediterranean anemia
B Anemias due to immune body type of hemolysin
  1 Acquired hemolytic anemia
  2 *Hemolytic disease of the new born*
  3 Paroxysmal hemoglobi ur a
C Hemolytic anemia associated with extr n c factors or di ease states
  1 Parasitic infections of red blood cells (malaria aroya fever) Action of lytic substanc s (Bacillus welchii toxin phenyl hydrazine)
  3 Hype ensitivity to drugs (sulfan lamide) or to other ub stances (favism) or to infectious processes (blackwater fever)
  4 Association w th d ease states but cause undetermined (lym phoma leukemia metastatic cancer)

Hemolytic anemia may usually be recognized as con genital by overt signs of hemolytic anemia in other members of the family or by spherocytosis of erythro cytes in relatives and increase in osmotic fragility of the patient s red cells and possibly those of other members of the family Red blood cells of patients with this dis ease are particularly susceptible to stasis both in test tube experiments and in the spleen Stasis of blood promptly increases spherocytosis and also the osmotic and mechanical fragility of the red cells After splenec

(5) Cal f M d 0 44 51 Ap 1 1949

tendencies which cause clinical and pathologic manifestations of this disease result from the fact that sickling decreases sedimentation rate and increases viscosity and mechanical fragility of red cell

Tests for sickling require production of reduced hemoglobin Two recent independent studies have used reducing agents The technic described here was evolved after testing many such substances

TECHNIC —A small drop of blood is placed on a slide mixed with 1 or 2 drops of 2 per cent sodium metabisulfite ($Na_2S_2O_5$) solution and covered with a glass cover slip Pressure is momentarily exerted to extrude excess blood and produce a film thin enough for examination of individual red cells with the high power dry objective of the microscope Sealing of the cover slip is unnecessary Sickling appears in 15 30 minutes

Because formalin* is a reducing agent it has been assumed that sickled red cells in tissues fixed with formalin* are sickled by its action Sickled red cells in capillaries of formalin* fixed tissues is evidence of a sickle cell trait but does not necessarily demonstrate that sickling occurred during life In such tissues sickling may have been an agonal event In contrast Zencker s fluid causes sickled red cells to revert to normal form and therefore tissues of patients with sicklemia fixed with Zencker s solution may not usually show sickled red cells

[For convenience in making a freshly prepared 2 per cent solution of $Na_2S_2O_5$ a 200 mg tablet of this substance may be dissolved in 10 cc distilled water Such tablets are available from Eli Lilly and Co —Ed]

HEMOLYTIC ANEMIAS

The articles summarized in this section deal with anemias in which increased red cell destruction is the predominant abnormality The increased breakdown of hemoglobin is usually reflected in increased bilirubinemia and excretion of stercobilin in the feces The compensatory response on the part of the highly active bone marrow is reflected in its hypercellularity and in sustained reticulocytosis in the peripheral blood The circulating red cells are never hypochromic unless there is an accompanying disturbance of hemoglobin synthesis as probably exists in sicklemia and Cooley s anemia Beyond this brief generalization are inadequate to describe the uncertainties concerning the nature and es of many

a sealed tube of clotted blood at 37 C Susceptible cells are hemolyzed as carbon dioxide accumulates whereas normal blood does not hemolyze Administration of al kali such as sodium bicarbonate temporarily delays hemolysis and transfusions are of considerable benefit since transfused cells are not hemolyzed The authors successfully treated one patient by repeated transfusions over a period of many years Splenectomy is of no benefit

Mediterranean anemia likewise has been treated suc cessfully by transfusion of normal cells It is thought to result from a structural defect of the red blood cells In some patients splenectomy has diminished severity of the hemolysis [data questionable —Eds]

In contrast to the normal survival of transfused red blood cells in patients with congenital anemias of various types normal cells transfused into patients with ac quired hemolytic anemias are rapidly destroyed Among 12 patients studied by the authors survival time of trans fused cells was determined in 5 in all of whom red cells were destroyed at an abnormally rapid rate In one pa tient the transfused cells acquired an increased hypotonic fragility within 24 hours after transfusion

By means of the Coombs test which was reported by its originator and subsequently by other workers to dif ferentiate congenital and acquired hemolytic anemia the authors demonstrated sensitization of circulating red cells by an immune body in nine patients with acquired hemolytic anemia They developed a technic for quanti tating the amount of antibody on the cell and found that activity of the hemolytic process is correlated with the amount of antibody present on the cell surface

Nine patients have undergone splenectomy with vari able results Four have exhibited complete clinical remis sion for periods of 18 24 months One had a remission of 18 months but died in relapse Four probably received some temporary or lasting benefit but the hemolytic process continued actively One patient died of anemia and two died of infectious processes not connected with

tomy most of the fragile cells disappear and osmotic fragility becomes more normal [as does the mechanical fragility —Eds] Normal cells given to patients with congenital hemolytic anemia are not hemolyzed at an abnormal rate but survive the normal time Normal cells transfused into patients with this disease show no tendency to increased osmotic or mechanical fragility after exposure to the patient s circulation Though it has always been assumed that the hemolytic' crises in this condition result from sudden acceleration of blood destruction recent work suggests that crises may result, rather from temporary aplasia of the bone marrow This assumption is based chiefly on the finding of low reticulocyte counts in the 10 14 days after crises Crises are therefore assumed to result from sudden decrease in blood formation rather than increased destruction. Splenectomy is thought to be effective in this disease because the spleen provides the principal site of stasis of red cells and development of fragile spherocytes

Sickle cell anemia is confined almost entirely to the Negro race and sickle cell trait is found in about 10 per cent of Negroes The chronic anemia and sudden hemolytic crises result from sickling of erythrocytes in capillaries and venules with consequent obstruction to blood flow and sometimes thrombosis Transfusions by increasing the patient s blood count slow down blood regeneration and therefore diminish the percentage of cells subject to destruction [They also by dilution decrease the increased mechanical fragility of the sickled erythrocytes —Eds]

Paroxysmal nocturnal hemoglobinuria is a chronic hemolytic anemia in which red cell destruction is increased during sleep thus usually at night This is thought to result from a tendency of the red blood cells to hemolyze in a slightly acid medium Accumulation of carbon dioxide during sleep causes relative acidosis which precipitates symptoms Hemolysis need not be sufficiently severe to cause hemoglobinuria A simple presumptive test for acid hemolysis consists ncubating

genic reactions The Hr factor is an agglutinogen which apparently has a reciprocal relationship to Rh Either one or both factors must be present in everyone both factors are never absent Consequently an Rh negative person must be Hr positive whereas an Rh positive person can be either Hr positive or Hr negative

In 23 Rh positive patients having febrile reactions and evidence of post transfusion hemolysis 17 were Hr negative whereas among 10 patients who had febrile reactions but no evidence of hemolysis none were Hr negative This indicates that Hr sensitization plays a predominant role as a cause of hemolytic reactions in Rh positive patients Hr antibodies were clearly demonstrable in the serums of only 3 of the 17 presumably sensitized patients This indicates that Hr sensitization when it occurs is usually mild a conclusion borne out by the usual mild course of reactions caused by Hr sensitization Such reactions are usually so harmless that they are passed off as ordinary pyrogenic reactions but they may sometimes endanger the patient s life as was demonstrated by the fact that one of the three patients with demonstrable antibodies died

Whereas routine pretransfusion Hr typing is still not practicable one should at least investigate every patient who has a febrile reaction for evidence of hemolysis If hemolysis has occurred even though the patient is Rh positive Hr tests should be done and if the patient is found to be Hr negative only Hr negative blood of a compatible blood group should be used for future transfusions

Eventually blood transfusion practice should include suitable precautions to avoid sensitization against the Hr factors as well as the Rh factors particularly in women to avoid birth of babies with erythroblastosis caused by Hr sensitization

How Important Is Transfusion as a Cause of Hemolytic Disease of the Newborn? To answer this question George Discombe and H O Hughes[7] (Central Middlesex

( ) B t M J 3 933) A g 14 1948

the hemolytic anemia One patient is alive and ambulatory with chronic hemolytic anemia six years after splenectomy

Recent work has made it possible to predict the occurrence of hemolytic disease of the newborn before birth so that replacement transfusion apparatus can be arranged for before delivery The authors have had excellent results with this treatment success presumably being due to removal from the circulating blood of the destructive antibodies causing the anemia [See following articles —Eds]

The next five articles are concerned with sensitization to the Rh factor —Eds

Intragroup Incompatibility with Respect to Hr Blood Factors as a Cause of Minor Hemolytic Transfusion Reactions is discussed by Alexander S Wiener[6] (Jewish Hosp of Brooklyn) Inclusion of Rh testing with A B blood grouping tests as a basis for selection of blood transfusion donors has virtually eliminated dangerous or major hemolytic reactions as a complication of transfusion Simultaneously post transfusion chills have become less frequent as methods of eliminating pyrogenic materials from blood transfusion apparatus have been perfected Virtual elimination of pyrogenic reactions has served to make more prominent another class of mild hemolytic reactions occurring in Rh positive patients sensitized by repeated transfusions given over a long period

It is recognized that Rh positive as well as Rh negative persons can be isosensitized because of the existence of more than one variety of Rh factor and the so called Hr factors Luckily these other blood factors are far less antigenic than the original rhesus factor (Rh_0) When isosensitization does occur it hardly ever reaches the degree characteristic of Rh_0 or AB sensitization so that antibodies usually are not demonstrable in the sensitized person s serum and reactions to transfusions of incompatible blood are mild and simulate pyro

(6) J L b & Cl Med 33 995 997 A gu t 194

resulted from occlusion of peripheral capillaries or larger vessels by agglutinated red blood cells and fibrin Regional to areas of vascular occlusion overlying epithelium showed degenerative or necrotic changes and in places erosion associated with hemorrhage from the fetal circulation into regional intervillous spaces

In all cases the blood clots associated with erosions of villi and trunks were of variable size and shape At times they were very small and covered the area of erosion only Frequently however especially when the vessels of trunks were involved they extended for some distance and in all directions from their source They bound villus to villus villus to trunk trunk to villus and occasionally trunk to trunk In placentas showing early changes red blood cells enmeshed in fibrin were identified and the adherent clots were irregular in shape Soon however most clots appeared to be molded into shapes resembling portions of villi and trunks the enmeshed cellular elements disappeared and the masses appeared as cylinders of fibrin These were apparently quickly covered by syncytium growing from areas near the injury and from the villus villi or trunk to which they were adherent Later connective tissue from regional structures grew into the fibrin cores and the completed structures were then indistinguishable from similar residual elements of the placenta

Since it is now known that the erythroblastosis in this disease is a secondary manifestation the designation erythroblastosis fetalis is no longer justified in Kline s opinion Furthermore since destruction of the incompatible fetal red blood cells in the disease occurs in part by phagocytosis congenital hemolytic anemia is not entirely accurate Transplacental erythrocytotoxic anemia is suggested as a better name for the disease

Value of Coombs Test in Detection of Isosensitization of the Newborn Rachel Jakobowicz Vera I Krieger and R T Simmons[9] (Melbourne) performed the direct Coombs test on 1 580 specimens of umbilical cord blood

(9) M J A t l 2 143 150 A g 7 1948

County Hosp) questioned 25 women who had had children with erythroblastosis fetalis and 200 women whose children had not had erythroblastosis fetalis for a history of blood transfusion given without Rh matching. Among the 25 mothers 9 (36 per cent) had been given transfusions without Rh typing. Among the 200 only 4 (2 per cent) had received such transfusions. It is concluded that erythroblastosis fetalis is 18 times as common in children of women who have been given transfusions without Rh typing as it is among children of women who have not been sensitized to Rh factors in this manner. Transfusion was thought to have been the cause of the erythroblastosis fetalis which developed.

It is the authors' policy to give blood to women under 40 only after Rh typing. If the patient's blood is Rh negative she must be given Rh-negative blood. In emergencies when transfusion must be given without Rh typing Rh negative blood is used.

Since sensitization can be induced by a single injection of a small quantity of antigen the authors have substituted a vitamin K analogue for intramuscular injection of blood in treatment of hemorrhagic disease of the newborn. Their calculations indicate that over 6 per cent of all infants given the latter treatment may thereby be sensitized to Rh antigen.

Microscopic Observations of Placental Barrier in Transplacental Erythrocytotoxic Anemia (Erythroblastosis Fetalis) and in Normal Pregnancy by B. S. Kline[8] (Cleveland) showed numerous breaks in placental villi permitting free interchange of maternal and fetal blood. These breaks observed in placentas of 15 cases of erythroblastosis fetalis and in 213 normal placentas of the second half of pregnancy were associated with hemorrhage from the fetal circulation into maternal intervillous spaces. In areas of recent hemorrhage nucleated red blood cells of the fetus were observed in regional intervillous spaces. Breaks in the placental barrier involved the surface of villi and trunks and apparently

(8) Am J Obst & Gynec 56 2 6 237 Aug 1 10

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(9) M J A t I 143 150 A g 7 1948

of newborn babies and the indirect Coombs test on 45 specimens of maternal serum and on 9 of cord serum

This method of testing for incomplete Rh antibodies and for weak Rh agglutinins is based on the fact that rabbit antihuman globulin serum agglutinates red blood cells which have absorbed Rh antibodies onto their surface in vivo or in vitro It is thought that the rabbit antihuman serum reacts with the globulin of the absorbed antibody In the direct test cells suspected of having been sensitized are exposed to immune rabbit serum which causes agglutination if the cells have absorbed antibody In the indirect test serum suspected of containing antibody is mixed with normal cells which are subsequently tested with immune rabbit serum

Although the direct test is primarily used in investigations of Rh sensitization it is not completely specific for Rh antibodies and a positive reaction indicates only that the red cells are sensitized by an antibody capable of reacting with the rabbit antihuman serum Thus the direct test successfully differentiates acquired hemolytic icterus from the congenital type The former condition is probably due in most cases to some form of immunization which results in a positive response to the direct Coombs test [Also see article by Wagley *et al* (p 357) —Eds] The indirect test is used to detect Rh antibodies in serum of mothers or newborn babies

Results of the authors use of the direct Coombs test indicate that it is slightly more sensitive than other methods of detecting Rh immunization but that occasional false positive reactions occur If the direct Coombs test is negative on the first day of life the infant is not likely to manifest erythroblastosis even if there are Rh antibodie in the mother s serum

The direct Coombs test was positive occasionally in cases of ABO incompatibility between mother and child In two of the three cases of this type of incompatibility in which the Coombs test was positive the child had jaundice or anemia or both A positive result to the Coombs test therefore constitutes warr ' the po s'

bility of development of clinical manifestations of hemolysis

In some cases the direct Coombs test may reveal that the apparent Rh negative status of the newborn infant s blood is due to coating with Rh blocking antibodies The indirect Coombs test is useful in confirming presence of small concentrations of antibodies in the mother s or infant s serum

Studies on Rh Hapten are reported by Bettina B Carter[1] (Pittsburgh) The term hapten is used to distinguish from complete antigens their specifically reacting fractions Thus a hapten combines with antibody in vivo and in the test tube but alone it does not produce antibody when injected into an animal

Rh hapten can be prepared by relatively simple methods Cells of outdated bank blood are pooled (plasma removed) and laked by mixing with distilled water The pooled cells are washed with descending concentrations of alcohol and filtered with suction through a Buchner funnel after each washing Powder obtained from the last filtration is mixed with ether allowed to stand five days and then filtered The ether filtrate is evaporated and drying completed in a desiccator The waxy residue contains active material

Assay of Rh hapten makes use of several serologic methods Determination of its potency depends on its behavior as an incomplete antigen in in vitro tests The most usable method involves complement fixation Another method uses specific inhibition of agglutination by the hapten It seems desirable to establish a standard for measuring activity of the Rh hapten With this standard a unit may be defined as the least quantity of Rh hapten required to fix 2 full units of complement in the presence of an anti Rh_0 (anti D) serum with antibody titer of 32 units

Rh hapten is apparently a lipid substance Failure of this substance to produce antibodies when injected into 96 guinea pigs indicates its hapten nature It produces

antibodies in animals only when coupled with an anti genic protein such as egg albumen As mentioned the hapten inhibits agglutination by Rh antibody in the test tube and fixes complement in its presence That a similar combination of Rh hapten with antibody occurs in vivo seems to be demonstrated by the fall in antibody titer after hapten injections

Rh hapten has been used clinically in both active and passive Rh sensitization Preliminary observations should be interpreted conservatively From 500 to 1 500 units of Rh hapten have been introduced intramuscularly at one time in treatment of Rh negative mothers whose blood contained Rh antibodies Initial injection may be followed by others in one or two weeks and at intervals throughout pregnancy Consecutive titrations of serum drawn from 30 treated sensitized women showed the ex pected falls in titer in all but 2 Treatment is begun preferably as soon as pregnancy is established in known cases of Rh sensitization and as soon as sensitization is revealed in pregnant Rh negative women who have had no previous difficulties due to the Rh factor No un toward reactions either systemic or local have resulted There is no evidence that the hapten is antigenic in hu man beings All but two babies of treated women were normal

Erythroblastotic babies i e those born of untreated Rh sensitized mothers have been given 1 000 1 600 units of Rh hapten at a time intramuscularly Of 25 severely affected babies treated 19 recovered and are developing normally In five of the six babies who died physicians believed that cause of death was not erythroblastosis

Mechanism of action of Rh hapten is not known Whether it neutralizes antibody or satisfies antibody re ceptors only further investigation will determine

[If this report indicates the possibility of a successful prophylac tic treatment for erythroblastosis fetalis its enormous importance is apparent To date however confirmation of these observations by other workers is by no means consistent Consequently undue optimism is at present unwarranted —Eds]

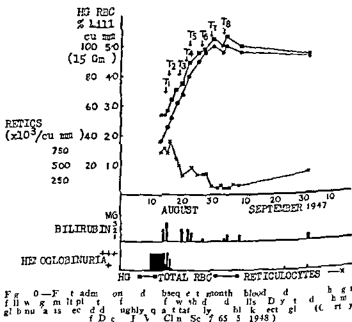
Transfusion of Saline Washed Red Cells in Nocturnal Hemoglobinuria (Marchiafava Micheli Disease) is recommended by J V Dacie[2] (Postgrad Med School London) Nocturnal hemoglobinuria is a rare hemolytic disorder usually lasting years in which there are episodes of hemoglobinuria mostly at night alternating with asymptomatic periods in which the hemolytic process continues but is less active Cause of increased hemolysis in this disorder is not understood but it is thought to lie in the patient s red cells which are sensitive to complement like hemolytic factors normally present in all human serum In vitro studies show that patients washed cells hemolyze readily in their own serum or in the serum of normal persons when slightly acidified No hemolytic substance has been found in patients serum or plasma Dacie describes beneficial effects of transfusion of saline washed red cells to patients with nocturnal hemoglobinuria Transfusions of washed red cells after periods of hemoglobinuria lasting in one patient for four months and in the other for three weeks were followed by remission of hemoglobinuria

CASE 1 —Woman 43 with known nocturnal hemoglobinuria for seven years was hospitalized because of persi tent hemoglobinuria for four months She was given washed cell derived from 4 400 ml blood during 23 days In this period she had no subjective symptoms or signs suggesting increased rate of hemolysis except on one occasion when she was given two bottles of washed cells the same day During treatment hemoglobin increased from 50 to 102 per cent red cell count increased from 1 700 000 to 4 700 000/cu mm reticulocyte count fell from 37 to 1 3 per cent and plasma bilirubin value fell from 2 mg to 0 5 mg per cent She was discharged f eling well Transfused blood cells were destroyed in a linear fashion and she remained asymptomatic until after two months hemoglobin level had fallen to 82 per cent and red cell count to 3 520 000 At this time she was readmitted because of moderate nocturnal hemoglobinuria for two days Washed cell of three additional bottl s of blood were given without reaction and she was discharged three day later She then had five days of hemoglobinuria which subsided spontaneously

( ) Cl S 7 65 75 1948

Six months later she was hospitalized and given two plasma transfusions without unfavorable reaction but after a transfusion of 13 day old blood she became nauseated and dizzy and passed almost black urine Intense hemoglobinuria persisted about 12 hours and then spontaneously disappeared

CASE 2 —Man 44 with paroxysmal nocturnal hemoglobinuria was given saline washed cells derived from 4 400 ml blood with the results illustrated in Figure 70 The multi



F g 0—F t adm on d bseq e t month blood d h g s f ll w g m lt pl t f f w sh d d lls D y t d h m gl b nu a is ec d d ughly q a t tat ly bl k ect gl (C rt y f D c J V Cl n Sc 7 65 5 1948)

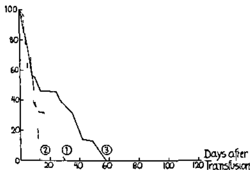
ple transfusions designated as T_1 to T_8 caused a rapid rise in red cell count and hemoglobin concentration a concomitant fall in reticulocyte count and serum bilirubin concentration and disappearance of hemoglobinuria Transfusion of washed cells gave similar results when the patient was again hospitalized four months later because of hemoglobinuria

Diminution in hemolysis in these patients after transfusion with washed red cells is considered largely due to reduced production of the patient s own abnormal red cells following relief of anoxia Since normal cells survive well after transfusion anemia may be corrected by

transfusion at intervals and patients kept in fair health

[In practice it is not usually necessary to u e wa hed red cell for transfusions in such patients Our experience indicates that fresh compatible citrated blood i generally satisfactory —Eds]

Life Span of Sickle Cell and Pathogenesis of Sickle Cell Anemia The various hemolytic syndromes may be classified into two main groups one comprising disorders in which red cells are damaged by an extracorpuscular mechanism (e g malaria) and the other of disorders in which premature disintegration of erythrocytes is ap



F g 71 —T f on f kl ll m ll t p t w th kl ll t t p d p t f g d ll (C t y f S g K t l J L b & Cl M d 33 975 984 A g t 1948)

parently caused by a primary abnormality of the stroma (e g familial hemolytic jaundice) This classification is based on cross determination of red cell survival time When normal erythrocytes transfused into a recipient with a hemolytic syndrome survive normally whereas the recipient s own red cells transfused into a normal person have a considerably shortened life span an intra corpuscular anomaly may be suspected Contrariwise when normal red cells transfused into a patient with a hemolytic syndrome are as rapidly destroyed as the patient s own cell an extracorpuscular mechanism may be assumed

Mechanism responsible for development of sickle cell anemia is not understood Only relatively few Negroes

who harbor the sickle cell trait are afflicted with this hemolytic syndrome Karl Singer Sidney Robin Joseph C King and Ronald N Jefferson[3] (Chicago) report cross determinations of survival time of sickle cells Trait cells were transfused into patients with sickle cell anemia and anemia cells into healthy recipients displaying the sickle cell trait

When trait cells were transfused into three patients with sickle cell anemia survival time of trait cells was normal (average 120 days) When red cells from four patients with sickle cell anemia were transfused into *three patients with sickle cell trait survival time* of anemia cells was shortened (Fig 71) Therefore the pathogenic principle operating in sickle cell anemia is within the red cells themselves It follows that trait cells can be safely used for therapeutic transfusions

Analysis of known facts about the sickling phenomenon shows that the sickling process which is the expression of an abnormality of the stroma does not yield a satisfactory explanation of the pathogenesis of the anemia The hypothesis is formulated that sickle cell anemia develops because of an additional alteration in the cytoskeleton which is qualitatively different from the structural anomaly responsible for the sickling phenomenon

[With this we could disagree because of the following established facts (1) The trait cell requires a much lower oxygen tension for production of sickling than does the red cell of the anemia patient (Sherman) (2) In anemia patients red cells are greatly increased in mechanical fragility when sickled but when not sickled they are normal in mechanical fragility (3) Moreover the mechanical fragility of completely sickled trait cells is less than that of cells from anemia patients (4) Thus to suppose that the mechanical fragility of the cell would determine its survival time allows the conclusion that the trait cell would not be as liable to sickling (and to increase in mechanical fragility) in traversing tissue capillaries as would the cell of the active disease (5) The hemoglobin of the sickle cell differs in several of its properties from that of the normal red cell (Pauling) See also the next article —Eds]

Sickle Cell Disease Studied by Measuring Survival of Transfused Red Blood Cells Sheila T E Callender

(3) J Lab & Cl Med 33 975 984 Aug 1948

James F Nickel and Carl V Moore (Washington Univ) and E O Powell[4] (Oxford England) report experiments designed to study the pathogenesis of increased hemolysis in patients with sickle cell anemia to determine how sickle cell anemia and sickle cell trait erythrocytes differ in terms of survival time following transfusion and to search for evidence that forms of sickle cell disease intermediate between the anemia and the trait might exist Survival of transfused red blood cells was measured with the Ashby technic of differential agglutination

When normal red blood cells were transfused into three patients with sickle cell anemia survival times of transfused cells were normal

When four normal subjects received blood from patients with sickle cell anemia in each instance there was a rapid destruction of the majority of transfused cells Graphs of survival however differed from those found in conditions which cause indiscriminate destruction of red cells e g in patients with acquired hemolytic anemia transfused with normal cells The rapid initial fall was not maintained and a small proportion of sickle cells tended to survive for a longer period When five healthy Negro subjects having the sickle cell trait were used as donors results were in striking contrast Four of five normal recipients showed normal survival of transfused trait cells Cells from the fifth donor showed a slightly shorter survival time the recipient in this instance did not report regularly and data are not entirely satisfactory

In one patient with sickle cell anemia who received blood from a donor with sickle cell anemia the disappearance of transfused cells was comparable to that in normal subjects This patient was given a second transfusion from another donor with sickle cell anemia This time oxygen inhalation (80 per cent initially 70 per cent from the second day) was started about 2 hours before transfusion and continued for 10 days Results are shown

(4) J L b & Cl M d 34 90 104 J y 1949

in Figure 72 Destruction of transfused cells, although abnormally rapid during the first 10 days was slower than on the occasion of the previous transfusion when no oxygen was administered When oxygen was discontinued cell destruction was accelerated indicated by a considerable increase in slope of the graph This increased slope compares well with the initial slope in

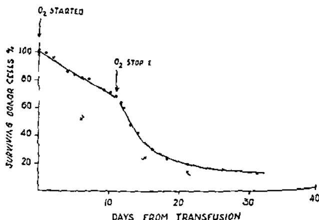


Fig 72 —Effect f yg n hal t on o v al of t f ed kl D h d r e h w l co t ol p t yg n gi (C te y f C ll d S T E t l J L b & Cl M 1 34 90 104 Ja f 1949)

the control recipient given blood from the same donor but not given oxygen

An attempt to accelerate disappearance of cells transfused from a donor with sickle cell trait was made by giving a replacement transfusion to a boy with congenital heart disease and extreme cyanosis However survival time of transfused cells did not differ from that found in normal recipient subjects

Results indicated clearly that increased hemolysis in sickle cell anemia is a function of the abnormal erythrocyte itself It seems likely that the abnormal shape of the sickled cell makes it less able to tolerate trauma of circulation Thus if intravascular sickl ~ could be re

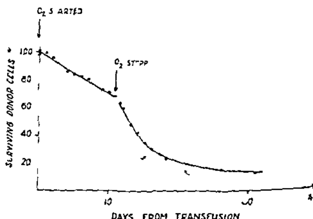
duced the rate at which cells from patients with sickle cell anemia are destroyed should be decreased It is not surprising therefore that erythrocytes transfused from a patient with sickle cell anemia seemed to survive longer in subjects who breathed high concentrations of oxygen

Though previous workers have suggested that ease of sickling is a function of age of cells and therefore that life expectancy of all cells in sickle cell anemia is reduced graphs of survival of transfused sickle cell anemia erythrocytes in this study showed a tendency for a proportion of cells to survive almost normally This suggests that while most cells in sickle cell anemia are constitutionally more susceptible to sickling and remain so until they are prematurely destroyed others are born more resistant and remain so throughout their existence According to this hypothesis sickle cell trait might be regarded as the extreme example of a state in which all cells are constitutionally more resistant to sickling Other reasons support the theory of a qualitative difference between sickle cell anemia and the trait (1) Patients with the trait show fewer circulating sickled forms even though most cells must be older than in sickle cell anemia (2) Transfused trait cells survive normally despite their average greater age and their ability to sickle (3) When trait cells are completely sickled by exposure to carbon dioxide and then subjected to mechanical trauma they are much less readily destroyed than are anemic cells under similar circumstances If the two types of sickle cell disease differ because of a qualitative difference in erythrocyte structure it is easier to understand why no clearcut examples of forms intermediate between the two have been described

Vascular Occlusion and Ischemic Infarction in Sickle Cell Disease The generally accepted concept of the pathology of sickle cell disease is that the abnormal shape of the sickled erythrocytes is responsible for stasis of blood flow in capillaries resulting in thrombosis and subsequent infarction Paul Kimmelstiel[5] (Charlotte

(5) A J M S 216 11 19 July 1948

in Figure 72 Destruction of transfused cells altho gh abnormally rapid durin, the first 10 days was slower than on the occasion of the previous transfusion when no oxygen was administered When oxygen was disco tinued cell destruction was accelerated indicated by a considerable increase in slope of the graph This in creased slope compares well with the initial slope in



F g 7 —Effe t f o ygen nhal t on o urv al of tr n fused ckle cells D hed cur e h w rvi al co trol ecip t o o ygen gi n (Coutesy of C llend S T E r l J Lab & Clin Med 34 90 104 J nuary 1949)

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Results indicated clearly that increased hemolysis in sickle cell anemia is a function of the abnormal erythro cyte it elf It seems likely that the abnormal shape of the sickled cell makes it le s able to tolerate trauma of circulation Thus if intravascular sickling could be re

re established at any one of these stages and ischemic infarctions may thus be found with or without thrombosis and with or without degenerative changes in the vascular wall

On the basis of Tomlinson s theory that sickle cell crisis is equivalent to preshock or shock crisis may be initiated by various factors which decrease oxygen in the peripheral blood Crisis is characterized by rapid blood destruction and increasing diminution of oxygen carrying capacity of red blood cells Peripheral vascular spasms may at least temporarily maintain normal blood pressure but also increase tissue anoxia leading to further sickling and introduction of a vicious cycle Peripheral vascular spasm may lead directly to ischemic necrosis in inner organs or be followed by capillary dilatation or stasis The engorgement of capillaries with sickle cells seen during this phase is regarded as a result rather than the cause of capillary stasi Local ischemia of ti sue and capillary walls may result in organic damage to vessel walls degenerative changes and thrombosis resulting in superimposed infarctions

Studies on Destruction of Red Blood Cells Spleen as Source of a Substance Causing Agglutination of Red Blood Cells of Certain Patients with Acquired Hemolytic Jaundice by Anti human Serum Rabbit Serum (Coombs' Serum) Serum from rabbits previously given injections of human serum (Coombs serum) agglutinates washed red blood cells of patients with acquired hemolytic jaundice but not the red cells of patients with congenital hemolytic jaundice Red cells are agglutinated presumably because of union of globulin or other substance on the red cell surface with the antibody of the test serum Because splenectomy in acquired hemolytic disorders sometimes decreases the agglutination titer of patient s red blood cells in Coombs serum Philip F Wagley Shu Chu Shen Frank H Gardner and William B Castle[6] (Boston) examined the spleens from persons with such disorders for substances with affinity for normal red

(6) J Lab & Cl M d 33 1197 1203 O t b 1948

N C) reports a case of uncomplicated sickle cell disease in which there were multiple foci of ischemic necrosis of inner organs without thrombotic occlusion of arteries

Negro girl 11 hospitalized with suspected diagnosis of poliomyelitis went into sickle cell crisis Because of the clinical picture of acute surgical abdomen and presence of gall stones the gallbladder was removed She died two days later The gallbladder showed ischemic necroses and autopsy revealed diffuse bilateral cortical necrosis of the kidney diffuse ischemic infarctions of the liver and multiple large foci of necrosis in the brain Changes in the brain resembled those of Schilder s encephalitis and those in the liver simulated changes in eclampsia Sickle cells and engorgement of capillaries were prominent but there was no vascular thrombosis The only condition to which all the clinical symptoms and pathologic changes could be attributed was marked sickling of red blood cells and anemia

Search of the literature for reports of arterial thrombi in sickle cell disease yielded surprisingly few conclusive reports [This of course would be the expectation because sickling would begin only where oxygen utilization began—beyond the arteriole in the capillary —Eds] The many types of morphologic change in this disease are not satisfactorily correlated One group of phenomena revolving around the hemolytic anemias include siderofibrosis of the spleen hemosiderosis of liver and kidneys relative frequency of gallstones and hematologic changes in peripheral blood and bone marrow The second group of phenomena are the circulatory disturbances Ischemic necroses of inner organs are often though not consistently found They may or may not be associated with organic changes in the vascular tree Degenerative changes in vessel walls endarteritis thrombosis and fat emboli have been described

In an attempt to correlate most of these circulatory phenomena Kimmelstiel hypothecates that the ischemic necroses in sickle cell disease are initiated by vascular spasm Vasodilatation may follow vascular spasm and stagnation of blood flow result in ischemic necrosis of vessel walls with subsequent thromboses Depending on the duration of the vascular spasm blood flow may be

It is concluded that spontaneous agglutination of red blood cells either causes or results from stagnation of these cells in the spleen Resulting injury to red blood cells is manifest in the increased osmotic and mechanical fragility of circulating red blood cells of most patients with acquired hemolytic disorders Such cells may well be abnormally susceptible to the trauma of the motion of the circulation

Hemolytic Anemia Associated with Atypical Hemag glutinins A case is reported by William J Kuhns and Philip F Wagley[7]

Negre s 43 was hospitalized in coma after 10 days vaginal bleeding History and examination revealed no gynecologic or other abnormalities except pallor and flame hemorrhages in the eyegrounds Response to transfusion was prompt and she wa discharged without further diagnosis

When she was seen a month later it was impossible to count red blood cell because of autohemagglutination A week later she was hospitalized because of progressive weakness and light jaundice Hemoglobin value was 2 9 Gm per cent Reticulocyte count was 21 per cent Osmotic fragility was nor mal Donath Landsteiner Ham and sickle cell tests were nega tive but cold agglutinins were present in a titer of 3 072 units She responded well to tran fusion but becaus repeated trans fusions were necessary splenectomy was performed A month after splenectomy cold agglutinin titer was 96 units and for the first time a warm agglutinin was present in a titer of 4 units During the five weeks after splenectomy she was given 10 L blood

She was discharged but readmitted a month later pro tr ite and markedly dyspneic Hemoglobin value wa 3 Gm per cent Hemagglutination was visible in the syringe u ed for veni puncture Cold agglutinin titer was 4 096 and warm agglutinin titer 64 units Two days later she died

Autopsy revealed cause of death to have b en massive intra vascular clotting in pulmonary vessels

Association of agglutination of red blood cells with increased fragility has previously been demonstrated Hemoglobinemia and hemoglobinuria have been pro duced in patients with high titers of cold hemagglutinins by exposure of a limb to cold These observations and those in hemolytic anemias of atypical pneumonia have

(7) A I t M d 30 4)3 4 3 F b 1949

blood cells Pulp from each spleen was incubated with normal red blood cells The cells were then separated from the splenic pulp and incubated with Coombs serum Results of these experiments are summarized in the table Spleens of patients with acquired hemolytic jaundice contained substances which caused red blood cells to agglutinate in Coombs serum whereas spleens of patients with congenital hemolytic icterus did not contain substances causing similar agglutination Spleens from patients with thrombocytopenic purpura Banti s syndrome and Gaucher s disease likewise did not contain substances with affinity for red blood cells

AGGLUTINATING EFFECTS OF ANTI HUMAN SERUM RABBIT SERUM (COOMBS SERUM ON WASHED NORMAL RED BLOOD CELLS AFTER INCUBATION WITH PULP OF SPLEENS FROM PATIENTS WITH VARIOUS DISEASES)

Cases	Diseases	Agglutination
1	Acquired hemolytic jaundice (lymphoid leukemia)	+
1	Acquired hemolytic jaundice (Boeck s sarcoid)	+
2	Acquired hemolytic jaundice (cause unknown)	+
3	Congenital hemolytic jaundice	0
4	Thrombocytopenic purpura	0
3	Congestive splenomegaly (Banti s syndrome)	0
2	Gaucher s disease	0

Ability of red blood cells to agglutinate Coombs serum may in fact be a test for absorbed serum globulin Possibly in acquired hemolytic jaundice the red blood cells act as an antigen and cause development in serum of antibodies with avidity for red blood cells However the nonspecific agglutination of red cells by antiserum developed in rabbits against type 14 pneumococcus or by viruses with which the animal has had no previous contact is too well known to permit interpretation of red blood cell agglutination in acquired hemolytic disorders as necessarily immunologic Perhaps the association of such agglutination with a variety of infections and neoplastic conditions (malaria tuberculosis Hodgkin s disease leukemia carcinomatosis and cysts and tumors of the ovary) favors the interpretation that there is nonspecific adsorption of a globulin substance by red cells

PERNICIOUS AND OTHER NUTRITIONAL MACROCYTIC ANEMIAS

Thi terminology is used to include macrocytic anemia that re spond either to the anti pernicious anemia principle of liver (vita min B ?) or to pteroylglutamic acid, irrespective of whether the nutritional deficiency is the result of defective diet or of gastric or intestinal dysfunction There is evidence that in several species—micro-organisms birds rats pigs and monkeys—vitamin B and pteroylglutamic acid have independent nutritional functions In human macrocytic anemias this separation may not be complete In addition to the clearly demonstrated nutritional deficiency wh ch causes maturation arrest in the bone marrow in pernicious anemia, there is a hemolytic element best measured by the survival time of the patient s red cells when transfused into normal persons There is however evidence from studies with isotopic nitrogen incorporated in glycine as a precursor of the porphyrin ring that the increased bile pigment output may be in excess by half of the actual rate of de struction of circulating hemoglobin It is obvious moreover that it is impossible for a patient to maintain a fairly constant degree of anemia as is often the case if sufficiently decreased production and increased destruction of red cells exist simultaneously—Ed

Life Span of Megalocyte and Hemolytic Syndrome of Pernicious Anemia There is general agreement that per nicious anemia is a deficiency disease and that liver ex tract corrects the deficiency However patients with addisonian anemia also show a severe disturbance of pigment metabolism There is usually mild retention jaundice and hemolytic index (urobilinogen excretion in feces correlated with total mass of circulating hemo globin) is far above normal

These abnormalities of pigment metabolism appar ently indicate a hemolytic process since they are also observed in other known hemolytic syndromes How ever in contrast to patients with other hemolytic dis orders persons with untreated pernicious anemia show no increase in reticulocytes of circulating blood If reticu locytosis is evaluated as a measure of red cell replace ment and high pigment output as an indication of simul taneously increased erythrocyte disintegration a con siderable imbalance in favor of erythrocyte destruction would be present in untreated pernicious anemia Conse

suggested to others that cohesion of erythrocytes may lead to their prompt mechanical destruction while in motion in the circulation Thus intravascular agglutination may conceivably have resulted in hemolysis in this case Ham and Castle have repeatedly suggested other mechanisms associated with red blood cell agglutination that would contribute toward or acutely cause hemolysis In this patient and in previous patients intravascular erythrostasis occurred in small vessels

Favism Albert P Rosen and James J Scanlan[8] (Providence R I) point out that although only five cases of favism have been reported in the United States the disease should be suspected as the cause of hemolytic anemia in persons of Mediterranean origin especially Italians and Jews since the bean is cultivated and eaten by such persons in the United States Favism is characterized by gastrointestinal complaints and sudden appearance of hemolytic anemia followed by hemoglobinuria jaundice and vascular collapse Symptoms occur minutes to a few hours after inhalation of the pollen or 5-48 hours after ingestion of the bean Pathogenesis of favism has been explained by three theories infectious, toxic and allergic A typical case follows

Boy 5 of Italian descent was hospitalized because of abdominal pain red urine and jaundice of 30 hours duration He had not been exposed to toxic fumes chemicals or malaria and had received no injections or transfusions There was no family history of anemia or syphilis A similar episode two years before had subsided spontaneously after two weeks

The spleen was palpated 5 cm below the costal margin The urine was packed with red blood cells Red cell count was 1 520 000 and hemoglobin value 38 per cent A blood smear showed red cells with marked central pallor anisocytosis poikilocytosis target cells and spherocytes Skull x rays were normal Cell fragility test was normal

He improved after a 500 cc blood transfusion and the fourth day temperature fell to normal The fifth day red cell count was 3 950 000 and hemoglobin value 75 per cent

It was then discovered that the patient had eaten four plates of fava beans the day before onset of illness and that he had eaten fava beans just before his attack two years previously

(8) N w E gl nd J Med 39 367 368 S pt 2

PERNICIOUS AND OTHER NUTRITIONAL MACROCYTIC ANEMIAS

This terminology is used to include macrocytic anemias that respond either to the anti pernicious anemia principle of liver (vitamin B ?) or to pteroylglutamic acid irrespective of whether the nutritional deficiency is the result of defective diet or of gastric or intestinal dysfunction There is evidence that in several species—micro-organisms birds rats pigs and monkeys—vitamin B and pteroylglutamic acid have independent nutritional functions In human macrocytic anemias this separation may not be complete In addition to the clearly demonstrated nutritional deficiency which causes maturation arrest in the bone marrow in pernicious anemia there is a hemolytic element best measured by the survival time of the patient s red cells when transfused into normal persons There i however evidence from studies with isotopic nitrogen incorporated in glycine as a precursor of the porphyrin ring that the increased bile pigment output may be in excess by half of the actu l rate of destruction of circulating hemoglobin It i obvious moreover that it is impossible for a patient to maintain a fairly constant degree of anemia as is often the case if sufficiently decreased production and increas d destruction of red cells exist simultaneou ly —Eds

Life Span of Megalocyte and Hemolytic Syndrome of Pernicious Anemia There is general agreement that pernicious anemia is a deficiency disease and that liver extract corrects the deficiency However patients with addisonian anemia also show a severe disturbance of pigment metabolism There is usually mild retention jaundice and hemolytic index (urobilinogen excretion in feces correlated with total mass of circulating hemoglobin) is far above normal

These abnormalities of pigment metabolism apparently indicate a hemolytic process since they are also observed in other known hemolytic syndromes However in contrast to patients with other hemolytic disorders persons with untreated pernicious anemia show no increase in reticulocytes of circulating blood If reticulocytosis is evaluated as a measure of red cell replacement and high pigment output as an indication of simultaneously increased erythrocyte disintegration a considerable imbalance in favor of erythrocyte destruction would be present in untreated pernicious anemia Conse-

quently peripheral blood should become rapidly depleted of erythrocytes resulting in early death Since clinically this process does not occur addisonian anemia has often been considered not to be a true hemolytic syndrome

The common denominator of all hemolytic syndromes regardless of causative mechanism is shortened life span of the cells involved To determine whether addisonian anemia may be classified as a true hemolytic syndrome survival time of erythrocytes from patients with untreated pernicious anemia was estimated by Karl Singer Joseph C King and Sidney Robin[9] (Michael Reese Hosp Chicago)

Red cells of two patients with pernicious anemia in relapse who had received no specific treatment for several months before the experiment were completely eliminated within 28 and 75 days respectively when transfused into a normal environment Profiles of their elimination curves were definitely abnormal and were similar to those caused by intracorpuscular abnormality of red cells in other hemolytic syndromes A third patient had had a few liver pills several days before hospitalization but otherwise had been untreated for three year When this patient s red cells were transfused into a normal recipient 68 per cent of transfused cells disappeared within 30 days and the remaining 32 per cent after 72 days (Fig 73) The biphasic character of the elimination curve profile supported the assumption that the blood contained two different populations of red cells namely red cells manufactured with participation of the liver principle and typical megalocytes produced in absence of the erythropoietic factor Red cells of a fourth patient with a blood picture normalized by continuou liver treatment for many years survived an average of 119 days when transfused into a normal recipient a normal value

These results indicate that red cells of patients with untreated pernicious anemia have a shortened survival time and that after adequate treatment the erythrocytes

(9) J Lab & Cl M 1 33 1068-10 6 Sept mbe 191

life span becomes normal Demonstration that survival time of the megalocyte is shortened permits classification of pernicious anemia as a true hemolytic syndrome Although the shortened survival time undoubtedly accounts for increased pigment production in this disease it is questionable whether it explains entirely the excessive production of pigment The absence of any considerably increased reticulocyte count in untreated pernicious anemia indicates that in this disorder erythrocytes

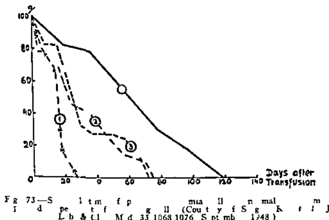


Fig 73—S 1 t m f p mia ll n mal m I d pe t f g ll (Cou t y f S g K t l J L b & Cl M d 33 1063 1076 S pt mb 1948)

are replaced predominantly by means of nonreticulated megalocytes

Demonstration that pernicious anemia is a true hemolytic syndrome in no way invalidates the concept that this disorder is a deficiency disease It is because of absence of maturation principle that defective red cells enter the circulation and are then eliminated more rapidly than normal ones

Observations on Relapses in Pernicious Anemia Edgar Jones Clifford C Tillman and William J Darby[1] (Nashville Tenn) observed 12 pernicious anemia patients carefully after discontinuing liver extract At time

r M d 30 374 380 F b y 1949

treatment was discontinued all were regarded as adequately treated having received from 420 to 1 020 units of liver extract at three to four week intervals during the preceding year Average red blood cell count during the year before treatment was discontinued was 4 740 000 for the seven men and 4 290 000 for the five women Because two women had rarely achieved red counts above 4 000 000 on adequate treatment although they showed no evidence of infection or other disorders known to inhibit response to liver extract it was impossible to consider as previously has been done a red count of below 4 000 000 as representing relapse Consequently it was decided to regard two successive counts of more than two standard deviations below the treatment mean for a particular patient as constituting relapse This allowed each patient to set his own relapse level in relation to his previously maintained values

According to these criteria relapse occurred in six patients 8 18 months after cessation of liver therapy The other six patients showed no relapse in 26 29 months without liver extract After this program had been under way 21 months it was decided to follow fecal urobilinogen levels as evidence of relapse Values were invariably normal when there was no anemia became elevated early during relapse and rose further as anemia progressed This indicates that hemolysis occurs early in relapse of pernicious anemia and emphasizes its importance in pathogenesis of this disease

No cause was apparent for differences in time required for relapse to occur in the patients observed Though number of patients is too small to permit conclusions it was noted that relapse occurred in five of seven men but in only one of five women No neurologic manifestations developed in any of the 12 patients during the observation period This is of interest in light of recent reports of a high incidence of neurologic disturbances in patients with pernicious anemia given folic acid and tends to confirm the suspicion that this vitamin actually brings about neurologic damage

Vitamin B_{12} Therapy in Pernicious Anemia Effect on Hemopoietic System Preliminary Report Byron E Hall and Donald C Campbell (Mayo Clinic) report hemopoietic responses of 11 patients with pernicious anemia in relapse to intramuscular administration of vitamin B_{12} Before treatment erythrocyte counts were less than 2 000 000 in eight patients and between 2 500 000 and 3 000 000 in three After administration of vitamin B_{12} reticulocyte peak counts were from 7 2 to 59 per cent in patients whose initial erythrocyte counts were less than 2 000 000 and from 2 1 to 9 7 per cent in the patients with higher initial counts In all patients reticulocyte peaks occurred from four to seven days after therapy began All reticulocyte peaks fell within range of expected response from liver therapy In four patients erythrocyte counts rose to normal in five to seven weeks in two the rise was more delayed In the remaining patients erythrocyte counts leveled off after counts exceeded 3 000 000 With increase in number of erythrocytes values for leukocytes and blood platelets returned to normal

Data collected in this and other studies suggest that *approximately 1 μg vitamin B_1 is equivalent to 1 U S P* unit of extracts of liver or stomach mucosa In two patients intramuscular administration of 1 μg vitamin B_1 daily induced maximal hemopoietic response a single large dose given after the initial reticulocytosis subsided failed to induce a second reticulocyte response Excellent hemopoietic responses were obtained in three patients given 25 μg once a week In two of these daily increment of erythrocytes ceased when the interval between injections was prolonged beyond 12 days

Sternal aspirations performed in 10 of the 11 patients revealed megaloblasts in 7 Marrow aspirations repeated during treatment showed erythrocyte regenerations from megaloblastic to normoblastic types 48 72 hours after administration of large amounts of vitamin B_1

( ) P St ff M t M y Cl 23 584 590 D 8 1948

Vitamin B_{12} Therapy in Pernicious Anemia Effect on General Clinical and Neurologic Manifestations Preliminary Report Byron E Hall and Donald C Campbell[3] (Mayo Clinic) describe clinical improvement in 11 patients with pernicious anemia treated with vitamin B_{12} Hematologic response is described in the preceding article Of 11 patients 6 had glossitis 3 had peripheral neuritis and 6 had peripheral neuritis and combined system disease Following administration of vitamin B_{12} a gradual return of strength and mental alertness and improvement in appetite with gain in weight were noted Soreness of tongue and mouth disappeared within a few days and regeneration of lingual papillae usually was complete within four to six weeks

Improvement occurred in eight of nine patients with neurologic disease Of the six patients with combined system disease five noted improvement in paresthesia and three had return of vibration sense Ataxia disappeared in three of five patients who had been affected Position sense of toes returned to normal in three of four patients The Romberg test which was positive in five patients before treatment became negative in two patients and results improved greatly in two Improvement in quadriceps femoris reflex occurred in one patient in another a positive Babinski reflex disappeared during treatment Severe mental depression disappeared in one patient

In the three patients with peripheral neuritis alone improvement occurred in 1 1½ months of treatment In three of six patients with more serious involvement improvement was unusually rapid

Observations on Etiologic Relationship of Achylia Gastrica to Pernicious Anemia Activity of Vitamin B_{12} as Food (Extrinsic) Factor is described by Lionel Berk and William B Castle (Harvard Univ) and Arnold D Welch Robert W Heinle Rudolph Anker and Martin Epstein[4] (Western Reserve Univ) Their observations

(3) Proc Staff Meet Mayo Clin 23 591 595
(4) New England J Med 239 911 913 Dec

on patients with pernicious anemia suggest that the extrinsic factor and the anti pernicious anemia principle of liver are identical and that the extrinsic factor does not react with the intrinsic factor as formerly thought but the intrinsic factor perhaps merely facilitates absorption of the extrinsic factor

That the extrinsic factor is identical with the anti pernicious anemia principle and that both are vitamin B_{12} was suggested by the following observations Hematologic response of patients with pernicious anemia in relapse to orally administered purified liver extract was potentiated by simultaneous administration of gastric juice Hydrolysis of the liver extract with sulfuric acid destroyed both its anti pernicious anemia and its extrinsic factor activity Parenteral administration of vitamin B_{12} produced hemopoietic and neurologic responses identical with those produced by liver extract Vitamin B_{12} was then found to be present in foods known to contain the extrinsic factor That vitamin B_{12} was able to act as extrinsic factor was shown by producing hematologic response in four patients with pernicious anemia in relapse by oral administration of vitamin B_{12} plus normal human gastric juice Such hematologic response could not be produced by oral administration of vitamin B_{12} without normal human gastric juice However the activity of the same amount of vitamin B_{12} on parenteral administration without gastric juice was even greater than on oral administration with gastric juice as was the activity of a 70 per cent alcoholic extract of beef muscle a classic source of extrinsic factor

The next two articles discuss the response of the glossitis in pernicious anemia to various therapeutic substances The first article describes the usual situation in which the glossitis though it may fail to respond in all instances to pteroylglutamic acid is favorably affected by purified liver extract or vitamin B The distinctly uncommon situation reported in the second article seems to be the failure of the glossitis to respond to treatment with highly purified liver extract and the subsequent success of treatment with various synthetic vitamins of the B complex including pteroylglutamic acid This can only be presumed to indicate a simultaneous deficiency of one or another of these vitamins It is to be recalled that these substances with the exception of calcium pantothenate

have been reported to relieve glossitis in deficiency states other than pernicious anemia —Eds

Response of Lingual Manifestations of Pernicious Anemia to Pteroylglutamic Acid and Vitamin B_1 Among their patients with pernicious anemia James F Schieve and R W Rundles[5] (Duke Univ) found two in whom pteroylglutamic (folic) acid therapy rapidly corrected glossitis despite the fact that it did not induce complete hematologic remission or prevent neurologic changes In contrast to these patients were six in whom folic acid failed to correct the glossitis of pernicious anemia In four of them subsequent treatment with liver extract [type unspecified —Eds] corrected the lingual as well as the other manifestations of pernicious anemia In the other two glossitis developed after administration of 30 and 50 mg folic acid daily for over two months In these two patients folic acid produced satisfactory hematologic and neurologic responses but because of the severity of the developing glossitis they were given a single injection of 0 025 0 05 mg vitamin B_1 Within a week lingual abnormalities disappeared

In an additional five untreated pernicious anemia patients lingual manifestations disappeared within five to seven days after injection of vitamin B_1 in a dose of 0 001 mg daily to 0 010 mg in a single dose

No explanation for the individual variability in therapeutic response in these patients is offered It is stressed however that folic acid has therapeutic limitations in treatment of glossitis of pernicious anemia just as it has in treatment of the neurologic and hematologic manifestations of this disease

Glossitis in Addisonian Pernicious Anemia Effect of Synthetic Vitamins of B Complex The fact that the sore tongue of pernicious anemia is indistinguishable from that occurring in well recognized nutritional deficiencies suggests that in pernicious anemia too it may be due to vitamin deficiency and that it may be corrected by appropriate treatment with one or more of the mem

(5) J Lab & Clin M d 34 439 447 Ap 1 1949

bers of the vitamin B complex Alexander Brown[6] (Univ and Royal Infirm Glasgow) observed seven patients with pernicious anemia and a well marked disturbance *suggesting deficiency of one or more members of the* vitamin B complex Diagnosis of pernicious anemia was based on a clinical picture compatible with the diagnosis macrocytic anemia with megaloblastic bone marrow re action which responded satisfactorily to treatment with highly purified liver extract histamine fast achlorhydria and absence of steatorrhea or dietary defect

Of the seven patients six had severe painful glossitis Five of the six had been receiving liver extract par enterally for from four months to two years and all re ceived it regularly every two to four weeks during the study Glossitis had either existed since the original ill ness or developed during treatment Development of a sore tongue was not always controlled by liver extract therapy and on occasion bore no relation to the patient s immediate or subsequent hematologic status In the sev enth patient glossitis was associated with angular stoma titis and vascularization of the cornea

These changes were controlled with single members of the vitamin B complex in pure form Four cases of glossitis responded to calcium pantothenate and one each to nicotinic acid and folic acid One case responded first to nicotinic acid and later to riboflavin The patient with glossitis angular stomatitis and vascularization of the cornea responded to riboflavin

Significance of glossitis in pernicious anemia is not understood but it is generally recognized that if sore tongue is a feature before treatment is begun it is usu ally cured by liver extract In the present series glossitis occurred without obvious relation to present or subse-quent blood levels Significance of this fact is not clear especially since others have apparently found such an occurrence rare It seems unlikely from what is known of the individual patients that exceptional dietary in adequacy was by itself responsible All had good appe

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6 1 704 706 Ap 23 1949

tites and were taking apparently adequate diets The possibility of a combination of minor defects of absorption in pernicious anemia and a suboptimal postwar dietary cannot be entirely discounted However it seems possible that development of a sore tongue in pernicious anemia reflects a breakdown in a metabolic system similar to that responsible for the megaloblastic marrow and the neurologic changes The fact that in this series the glossitis could be controlled by administration of synthetic vitamins suggests that the breakdown may involve the availability of the vitamin found effective

Cells of Megakaryocyte Series in Pernicious Anemia In Particular, Effect of Specific Therapy Robert D Epstein[7] (Harvard Univ) studied megakaryocytes of the bone marrow and platelet counts of peripheral blood before and after liver therapy in five patients with pernicious anemia Particular emphasis was placed on morphologic appearances and numbers of mononuclear megakaryocytes and polykaryocytes (megakaryocytes with multiple nuclei in a single cytoplasmic mass)

Before remission was induced by specific therapy number of polykaryocytes was increased and number of mononuclear megakaryocytes in bone marrow decreased whereas after remission induced with liver extract this ratio of cells was reversed Before remission 50 per cent or more of the megakaryocytes were multinuclear whereas after remission percentage of polykaryocytes varied from 0 to 11 2 per cent Conversely before treatment 25 50 per cent of megakaryocytes were mononuclear and after therapy 75 per cent or more were mononuclear In four of the five patients the increased number of polykaryocytes before treatment was associated with *low platelet counts in peripheral blood In the fifth* patient platelet counts were in the lower range of normal before treatment In each instance when the patient responded to therapy platelet counts in peripheral blood increased as number of polykaryocytes in marrow decreased

(7) Am J Path 25 239 51 March 1949



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There was no diminution of total number of megakary ocytes before treatment in two patients total megakaryo cyte count being above normal In three of the five patients percentage of megakaryocytes exhibiting ap

parent platelet formation was less in the specimen obtained before treatment than subsequently during remission There was however, no constant relationship between platelet counts in peripheral blood and total number and percentage of cells of the megakaryocyte series apparently producing platelets

It has been found that entirely without liver extract therapy a shift in the bone marrow from megaloblastic to normoblastic red cell formation sufficient to return the hemoglobin to normal occurs after blood transfusions in patients with pernicious anemia However there was no significant change in the megakaryocyte series with such transfusions

Though this interpretation is disputed it has been hypothecated that the polykaryocyte is an intermediate cell type which develops during formation of the mature megakaryocyte from fusion of primitive mononuclear cells Figures 74 and 75 illustrate young and intermediate polykaryocytes The young polykaryocyte contains four nuclei with fine chromatin and a basophilic cytoplasm in which there are a few scattered granules A few platelets are apparently being formed in one portion of the periphery In the intermediate polykaryocyte the seven nuclei show increased clumping This and the presence of small azurophilic granules in the cytoplasm distinguish it from the young polykaryocyte No platelet formation can be seen

Macrocytic Anemia of Pregnancy Refractory to Vitamin B_{12} Therapy Response to Treatment with Folic Acid Report of Case Although in certain patients with macrocytic anemia of pregnancy failure of treatment with purified liver extract has been reported such patients respond to oral administration of crude liver extract and as was shown after pteroylglutamic (folic) acid became available to this substance Lois A Day Byron E Hall and Gertrude L Pease[8] (Mayo Clinic) demonstrated that crystalline vitamin B_{12} highly effective in treatment of addisonian pernicious anemia was

(8) P c Staff Meet. May Cl n 4 149 157 M

like purified liver extract ineffective in a patient with macrocytic anemia of pregnancy who later responded fully to administration of pteroylglutamic acid

Woman 27 on a normal diet was well until the fifth month of her second pregnancy when several crops of aphthous ulcers appeared on the mucous membranes of the mouth and lips At the beginning of the seventh month of pregnancy she began to feel tired and nauseated vomited everal times during the day and had watery greenish stools Soreness and bleeding of the gums and soreness of the mouth but not of the tongue were noted During the next few days the feet legs hands and face became swollen dyspnea appeared on exertion appetite diminished and the hair became extremely dry and came out in handfuls An undetermined amount of blood was lost due to hemorrhoid Numbness or tingling of extremities was not experienced On admission a week later edema of the face and extremities was noted The skin appeared waxy and was pearly white in color Mucous membranes of the gums were brick red in striking contrast to the paleness of the tongue Temperature and blood pressure were normal and urinalysis negative Blood analysis revealed 6 5 Gm hemo globin 1 700 000 red cells and 3 500 l ukocytes with slight granulocytopenia Four per cent of the nucleated cells were normoblasts The reticulocyte count was 0 9 per cent Plate lets numbered only 39 000/cu mm Examination of bone mar row revealed hyperplastic marrow with megalobl astic erythro poiesis and active myelopoiesis

Parenteral administration of a liver extract containing 15 U S P units/cc (injectable) was begun and during the next 11 days the patient received a total of 135 units without hemo poietic or clinical response Three transfusions of 500 cc com patible Rh n gative blood were then given Gastric analysis showed free hydrochloric acid The stools contained 28 8 per cent fat Hemoglobin concentration was 9 2 Gm and red cells numbered 3 510 000 On the fifteenth day parenteral adminis tration of vitamin B_1 was started a total dose of 27 5 µg be ing given in eight days Two or three hours after each injec tion the patient became nau eated and vomited The general condition seemed worse during vitamin B_1 therapy On the thirty second day parenteral admini tration of pteroylglutamic acid was begun with an initial do e of 30 mg and continued with daily doses of 15 mg until delivery of a normal infant a month later On the sixth day of treatment with pteroylglutamic acid a reticulocyte peak of 18 per cent was rea hed Clinical improvement was dramatic Appetite increa ed greatly edema rapidly receded and diarrhea disappeared Hair and skin im proved in appearance and texture On the ninth day of treat

ment bone marrow puncture showed active erythropoie is of normoblastic type

Response of Tropical Sprue to Vitamin B_{12} in five patients in Puerto Rico is reported by Tom D Spies and Ramon M Suarez [9] All patients had macrocytic anemia megaloblastic arrest of bone marrow erythrocyte counts below 2 500 000 persistently low reticulocyte counts during the preliminary observation period and alimentary tract symptoms consistent with diagnosis of tropical

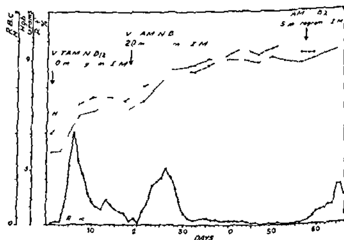


Fig 6—II m p t c p e f pat t w th t op al pru t tam n B (Co rte y of Sp s T D a d S a e R M Bl od 3 1213 12 0 N em b 1948)

sprue Either the patients were untreated or treatment had not been recent enough to interfere in any way with evaluation of vitamin B_{12}

Figure 76 illustrates the hematologic response to administration of vitamin B_{12} Reticulocytosis occurred in each case usually around the fourth day and was followed by erythrocytosis and hemoglobin production Clinical improvement characterized by gain of strength and great increase in appetite and feeling of well being occurred in four patients given 10 25 μg vitamin B_{12}

(9) Blood 3 1 13 1 0 No mber 1948

The fifth patient given only 4 μg showed little or no change Since in no instance was a maximal dose given these patients soon tended to relapse clinically and hematologically They could again be relieved promptly by another injection of vitamin B_{12} or by folic acid A single injection of approximately 100 μg vitamin B_1 would probably be needed to produce a full hematologic response in persons so ill

This tentative appraisal would suggest that vitamin B_1 per unit of weight is more effective in treating human disease than any compound that has yet been used

Crystalline Anti Pernicious Anemia Factor in Treatment of Two Cases of Tropical Macrocytic Anemia J C Patel[1] (Bombay India) administered a substance isolated in England and thought to be identical with vitamin B_1 to two patients with tropical macrocytic anemia

CASE 1—Man 42 was hospitalized because of an illness of 12 months duration characterized by passage of two or three stools daily flatulence left abdominal pain and burning of the mouth For three months he had had giddiness and palpitation and had been unable to work He was a vegetarian and recently had put himself on a starch diet because of indigestion Tongue was pale and smooth but physical examination revealed no other abnormality except pallor Urine and stools were apparently normal There was free hydrochloric acid in the stomach Red cell count was 1 690 000 hemoglobin 8 6 Gm per cent white cell count 4 100 mean corpuscular volume 140 cu μ and mean corpuscular hemoglobin concentration 36 per cent

Six days after injection of 80 μg crystalline anti pernicious anemia factor reticulocyte count was 11 5 per cent and after 14 days red count had increased to 2 560 000 hemoglobin value to 11 2 Gm per cent and white count to 6 500 Marrow examined before and seven days after injection showed a change from megaloblastic to normoblastic

CASE 2—Boy 16 was hospitalized because of weakness anorexia and stomatitis for two months He had had an attack of dysentery at age 10 and thereafter had had intermittent abdominal pain and diarrhea Examination revealed no abnormalities except pallor No significant parasites were found in stools Gastric analysis revealed free acid Red cell count was 1 760 000 white cell count 2 500 hemoglobin value 6 9 Gm

(1) B t M J 934 3 N 7 1948

per cent mean corpuscular volume 105 cu μ and mean corpuscular hemoglobin concentration 37 4 per cent Icterus index was 5 units He was given 80 μg crystalline anti pernicious anemia factor by injection and had a maximal reticulocyte response of 36 8 per cent the fifth day Appetite returned the third day The blood 15 days after treatment showed 2 560 000 red cells mean corpuscular volume 101 5 cu μ mean corpuscular hemoglobin concentration 36 5 per cent hemoglobin value 9 51 Gm and white count 4 600 Marrow which was megaloblastic before treatment was normoblastic six days after injection

[On the whole evidence indicates that patients with tropical macrocytic anemia fail to respond to purified liver extracts injected in usual amounts and tend to respond to autolyzed yeast or crude liver extract Consequently these responses to vitamin B are probably not characteristic of this group of patients —Eds]

HYPOCHROMIC ANEMIA

Hypochromic anemia unless caused by chronic infection or present in sickle cell disease or the milder form of thalassemia results from a lack of available iron in the body Inorganic iron is also the only curative agent required. The three articles in this section are concerned with this commonest form of anemia —Eds

Hypochromic Anemia is summarized by Maurice B Strauss (Harvard Univ) As the hemoglobin saturation of red blood cells decreases in hypochromic anemia their volume diameter and thickness decrease Stained blood films show variation in size and shape of red blood cells with pessary forms in which hemoglobin is concentrated at the periphery and target forms in which hemoglobin is concentrated both at the periphery and in the center

Flattening or spooning of fingernails commonly accompanies hypochromic anemia and has seldom been reported in patients without hypochromic anemia Such nails are soft and easily broken In patients with hypochromic anemia the papillae of the tongue are often atrophic but the tongue is rarely sore or red except in Plummer Vinson syndrome a condition characterized by hypochromic anemia glossitis spoon nails and dyspha

(2) Am. P t 3 (5 70 October 1949

gia from webs or bands in the hypopharynx and esophagus Splenomegaly may occur as in any long standing anemia Other symptoms and signs common in patients with hypochromic anemia are palpitation breathlessness weakness fatigability vertigo ankle edema and systolic murmurs

Studies indicate that adult males not losing blood excrete only about 1 mg iron daily in urine and feces This iron loss would lower normal hemoglobin only 15 per cent in a year if no iron were ingested Loss of 50 cc blood with each menstrual period plus fecal and urine losses would lower blood hemoglobin content in the average woman about 30 per cent in a year Iron loss in blood lost during delivery plus iron loss to the fetus is more than the amount normally lost in 10 menstrual periods

It seems unlikely that man can devise a diet containing less than 1 mg iron daily Consequently in adult males with hypochromic anemia not explainable by external bleeding Strauss insists on complete roentgen examination of the gastrointestinal tract for ulcers or tumors Negative results are followed by *frequent* stool tests for occult blood and x ray examinations are repeated several times for at least two years

Following are the factors commonly responsible for increased iron requirements

- I Increased blood volume—rapid growth
  - A Infancy
  - B Puberty
- II Normal blood loss
  - A Menstruation
  - B Parturient bleeding
- III Loss of iron for fetal blood building—pregnancy
- IV Pathologic bleeding
  - A Gastrointestinal
    - 1 Ulcer—esophagus stomach duodenal jejunal Meckel s diverticulum
    - 2 Varices—esophagus stomach
    - 3 Telangiectases
    - 4 Tumor — benign malignant — stomach small bowel colon biliary system

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(2) Am P ct 3 (5 70 October 1954

level was below normal both unsaturated iron binding capacity and total carrying capacity of serum were above normal In infection serum iron level was also reduced but iron binding capacity and total capacity were reduced as well In a variety of conditions having in common only general debility and reduction in plasma protein iron carrying capacity of serum was below normal Ten normal pregnant women showed no significant deviation from normal during pregnancy Serum iron level and percentage saturation of the iron binding protein were

AVERAGE SERUM IRON (S I) LEVEL, UNSATURATED IRON BINDING CAPACITY (I B C) TOTAL CAPACITY AND PER CENT SATURATION IN NORMAL AND ABNORMAL STATES

STAT	S I Mi og am /100 c	I B C M c og m /100 c	To M c o m /100 c	Satu n c
Normal (male)	106	205	311	34
Normal (female)	94	194	288	33
Iron deficiency anemia	29	319	346	9
Pernicious anem a	178	104	232	56
Infertion	44	176	220	20
Hemochromatosis	224	23	247	91
Liver dis ase	111	116	227	50
Transfusion hemosiderosi	260	0	260	100

high in refractory anemia pernicious anemia hemochromatosis transfusion hemosiderosi and liver disease

Fraction IV 7 from human plasma bound 1 mg iron/mg protein in vitro This substance was administered intravenously to 22 persons in 2 5 5 Gm amounts in 15 30 minutes In two patients injection was repeated after two weeks These injections produced slight rise in serum iron level during the first 4 6 hours but maximal rise followed a 12 24 hour latent period and totaled as much as 115 µg per cent This fell during the following two to six days except in patients who had hemosiderosis or hemochromatosis in them the elevation was maintained longer A second injection of globulin given the same patient did not produce rise in serum iron level except in cases of iron excess

5. Hiatus hernia
6. Parasites
7. Hemorrhoids

B Uterine
Menorrhagia metrorrhagia
C Urologic
D Nasal
E Bronchopulmonary
F Wounds

Chronic blood loss with adequate iron intake results in a normochromic normocytic anemia Though the precise effect of gastric achlorhydria on iron absorption remains unsettled some experimental work indicates that *iron is more rapidly absorbed from an acid than from an* alkaline medium

Ferrous sulfate 5 gr three times daily may be ex*pected to raise the red blood cell count 103 000/cu mm* and hemoglobin concentration 1 33 per cent daily In rare cases double this dose is required For small children it may be prescribed as an elixir or sirup To minimize gastric irritation all preparations are given after meals Need for parenteral injection of iron is rare There is no convincing evidence that copper manganese molybdenum liver extract, vitamin B or other medicament speeds regeneration of hemoglobin

Chemical, Clinical and Immunologic Studies on Products of Human Plasma Fractionation Serum Iron Transport, Measurement of Iron Binding Capacity of Serum in Man Using a microbiologic assay method Charles E Rath and Clement A Finch[3] (Harvard Univ) studied serum iron concentrations in different conditions *The* test used depends on ability of a β_1 globulin (molecular weight about 90 000) to develop a salmon red color when combined with iron

Average values for serum iron unsaturated iron binding capacity total capacity and per cent saturation in 30 normal subjects and 105 patients are shown in the table There were no *significant differences between* men and women In iron deficiency though serum iron

level was below normal both unsaturated iron binding capacity and total carrying capacity of serum were above normal In infection serum iron level was also reduced but iron binding capacity and total capacity were reduced as well In a variety of conditions having in common only general debility and reduction in plasma protein iron-carrying capacity of serum was below normal Ten normal pregnant women showed no significant deviation from normal during pregnancy Serum iron level and percentage saturation of the iron binding protein were

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Level of serum iron and per cent saturation of iron binding protein are well regulated under normal circumstances Bone marrow block iron excess and severe liver disease all increase saturation of iron binding protein Whether iron excess may occur without some degree of hepatic dysfunction is not yet clear

Intravenous Treatment of Anemia with Iron-Sucrose Preparation. In the attempt to find an iron preparation suitable for parenteral administration H G B Slack and John F Wilkinson[4] incubated solutions of various iron compounds with fresh human serum and observed them microscopically for evidence of flocculation Of the compounds tested only two were compatible with serum Of the two only one seitz filtered ferri oxidum saccharatum B P (1 per cent iron) could be given without causing symptoms of iron intoxication This substance was prepared as follows

METHOD —Anhydrous ferric chloride (5 8 Gm) is dissolved in distilled water (50 ml) in an evaporating dish on a water bath at 95 C and sucrose (28 Gm) added with stirring until dissolved Anhydrous sodium carbonate (1 8 Gm.) and sodium hydroxide (5 Gm) are dissolved separately in 25 ml water each Carbonate solution is added slowly to ferric chloride solution with stirring and carbon dioxide is allowed to come off after each addition Sodium hydroxide solution is then added The preparation is stirred for 15 minutes filtered through a Whatman no 42 filter paper into rubber-capped vials and immediately autoclaved at 115 116 lb./sq in. for 20 minutes

Total dose of iron given patients with iron deficiency anemia is 24 5 mg elemental iron for each 1 per cent deficit of hemoglobin plus 50 per cent The authors give 25 mg the first day 50 mg the second 100 mg the third and 200 mg the fourth and subsequent days but occasional patients require 200 mg twice daily Iron sucrose in 2 per cent solution was given from an all glass 5 or 10 ml syringe with no 2 stainless steel Record needles into antecubital veins at the rate of about 2 ml./minute

Of 60 patients treated only one had an unfavorable reaction to doses of 200 mg daily or twice daily Reac

(4) Lancet 1 11 13 Jan. 1 1949

tions to one 300 mg dose occurred in many patients

Of the 60 patients 10 had proved refractory to full doses of iron by mouth over long periods The reason for failure of oral therapy in these patients is not known but inability to absorb iron from the intestinal tract was postulated All these patients were women aged 20 50 and none had had excessive blood loss All had been pregnant and had had variable degrees of menorrhagia Thirty eight patients had had blood loss from uterus or intestinal tract and/or dietary deficiency and two had chronic infection without demonstrable blood loss

Small local venous thromboses occurred after only 4 of over 800 injections Hematologic and clinical responses were often as dramatic as those obtained when patients with pernicious anemia in relapse receive adequate doses of liver extract Utilization of intravenous ferric sucrose preparation was apparently almost 100 per cent Though initial responses to injected iron were good in patients with infection relapses occurred suggesting that in infection demand for iron by cell systems of the body is greatly increased

[Our own small experience with a similar preparation confirms its effectiveness in uncomplicated hypochromic anemia and its relative freedom from immediate toxic effects We are however unfamiliar with such high incidence (10 of 60 patients) of hypochromic anemia refractory to full dosage of iron by mouth Moreover in the light of present knowledge of the difficulty with which iron is excreted from the body and of the liability to development of hemosiderosis from parenteral iron given over a period in the form of transfusions we believe that these readily given preparations of iron for intravenous use present a similar though remote hazard Clearly therefore they should be used only on very real indication It has been estimated that the amount of liver extract given by injection by physicians in this country greatly exceeds that for which there is any real indication Except for the possibility of sensitization this is probably physiologically harmless albeit wasteful and costly to the patient The discovery of the satisfactory therapeutic activity of orally administered iron compounds especially the ferrous salts tended to inhibit to some extent the widespread custom of iron injections The local pain often produced was likewise a deterrent Let us hope that the availability of the iron sucrose preparations which are painless to inject will not lead to a recrudescence of a practice in the treatment of hypochromic anemia which was largely unnecessary and which there is reason to believe may be harmful to the patient at a later date.—Eds]

OTHER ANEMIAS

The articles in this section deal with anemias resulting from other than nutritional deficiencies —Eds

Hemosiderosis in Refractory Anemia Discovery of iron and liver therapy has brought into prominence a type of primary anemia which fails to respond to any known treatment and has therefore been referred to as primary refractory anemia It has been subdivided into four types according to histopathologic appearance of bone marrow These with their clinically comparable conditions are pseudoplastic anemia (partly mature cellular marrow) aplastic anemia or panmyelophthisis (hypocellular marrow) chronic granulocytopenia (immature cellular marrow) and myelosclerosis (fibrosis sclerosis and giant cell hyperplasia of marrow) With lack of specific therapy treatment is mainly by repeated *blood transfusions* *A dramatic observation in persons* with refractory anemia given multiple blood transfusions has been development of hemosiderosis of liver spleen and other organs

J P Wyatt and H Goldenberg[5] (Toronto) report that 3 of 16 autopsies in cases of refractory anemia with extramedullary hemopoiesis revealed notable hemosiderosis *The three cases had in common chronic marrow* disease with refractory anemia treatment with multiple blood transfusions and intense hemosiderosis in liver and spleen

Hemosiderosis (deposition of iron pigment resulting *from* destruction of red blood cells) must be distinguished from hemochromatosis the most important distinguishing *feature being the difference in distribution* of pigment in spleen bone marrow and kidneys Abundant pigmentation of these organs in hemosiderosis is *in* decided contrast to the sparse distribution in hemochromatosis Localization of pigment in hemosiderosis suggests

(5) A b I c M J M f 6 J y 1949

a hemolytic origin There is abundant evidence that an abnormal degree of hemolysis does not occur in hemochromatosis Hemosiderosis of kidneys however is not observed in patients with refractory anemia given repeated transfusions in sharp contrast to what occurs in conditions in which an abnormal degree of hemolysis has taken place

Pathogenesis of pigment deposition in patients with refractory anemia given multiple transfusions was not clear Clinical and laboratory evidence of increased destruction of blood was lacking in the authors patients No transfusion reactions occurred and no jaundice was observed The patients had no history of nutritional deficiency so that the cytosiderosis of malnutrition seen in patients with pellagra and the dietary hemosiderosis observed in rats seemed unlikely Siderosis is probably due mainly to disturbance in iron metabolism rather than to increased blood destruction Because of inability of diseased marrow to utilize iron ordinary slow destruction of red blood cells may result in accumulation of pigment which is deposited in storage depots of liver and spleen The fact that hemosiderosis does not occur in the kidneys is added evidence that the condition is not due to an abnormal degree of hemolysis and fits the theory that a storage phenomenon is involved Although the pathogenesis of pigment deposition has not been established attention should be drawn to the development of hemosiderosis in this age of multiple blood transfusions

[In the absenc of bleeding daily iron loss is probably less than 1 mg In Case 1 of the present report .8 transfusions (pres.imably of 500 cc whole blood each) were given in th five months bef r death This is equivalent to about 7 1 Gm iron or 2 Cm more than the total iron in the body of the normal per or Of tl i only about 150 mg would be xcreted t k ng the usual figure of 1 mg/day —Eds]

Myelofibrosis Associated with Tuberculosis Report of Four Cases Myelofibrosis is a disease in which the normal blood forming elements of bone marrow are replaced by fibrous tissue with compensatory extramedullary hemopoiesis arising in other organs of the reticulo endothelial system Among 91 cases of myelofibrosis re

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(5) A b I t M d 83 67 76 J y 1949

healed tuberculosis in each patient All ran a downhill course with progressive weakness wei ht loss and fever ending in death Duration of illness ranged from 12 to 18 months

At autopsy generalized caseating miliary tuberculosis was found in all organs Extramedullary hemopoiesis and an increase in megakaryocytes were evident in all ca es most commonly in spleen lymph nodes and liver Lymph nodes were enlarged and normal cellular elements were replaced by proliferating granulomatous tissue



Fg 77—A t p y ph t m g ph f b m w h w g t fib w th l ttl em g k mop et t (C t y f C l H W *et l* Bl d 3 14 f 1444 D mb 1948)

Bone marrow from sternum rib and vertebra in each case was replaced by varying amounts of connective tissue (Fig 77) Fibrosis and hyalinization of liver spleen pleura pancreas and adrenals were prominent

A comparison of these cases with five cases of idiopathic myelofibrosis revealed many common features In both the idiopathic and the tuberculous cases there were splenomegaly anemia leukemoid blood picture fibrosis in bone marrow with increase in megakaryocytes and extramedullary hemopoiesis However the idiopathic cases occurred in an older age group (53 77 years) there was no fever except terminally in one case spleens were larger and lymphadenopathy was less prominent Aver

ported in the literature were 7 with definite evidence of active tuberculosis Howard W Crail Howard L Alt and Walter H Nadler[6] (Northwestern Univ) observed four more such cases

All four patients presented typical complaints of pain in the long bones back or abdomen fatigue progressive weakness pallor and weight loss Ages were 29 50 All patients had a daily afternoon fever with occasional spikes to 104 F All had a moderately enlarged spleen and three a markedly enlarged smooth nontender liver Generalized lymphadenopathy was moderate in all patients Retroperitoneal lymph nodes were greatly enlarged in one patient and were palpable through the abdominal wall

All patients showed refractory anemia which was slowly progressive in three but became severe terminally In one patient anemia was profound and required frequent transfusion throughout illness A leukemoid reaction characterized by immature leukocytes and normoblasts occurred in all patients Three had progressive leukopenia but the fourth had a leukocyte count above 100 000 with differential count closely resembling that in acute myeloid leukemia Platelet count paralleled leukocyte count in all patients and reticulocyte percentages were normal Sternal marrow aspirations in two patients early revealed a hyperplastic marrow Later marrow became hypoplastic and material from sternal aspiration then resembled peripheral blood both in total and differential cell counts Single marrow aspirations in the other two patients revealed hypoplasia All marrow smears showed increase in megakaryocytes Bone marrow biopsy done on one patient revealed depletion of normal hemopoietic tissue and fat with beginning fibroblastic replacement and marked increase in megakaryocytes Bacteriologic and serologic studies were negative in three patients acid fast organisms were recovered from fluid aspirated from the chest late in the illness of the fourth patient X ray examination of the chest revealed old

(6) Blood 3 1426 1444 Decemb 1948

measured in 30 normal subjects Mean standard deviation was 359 $\pm$ 30 8 μg per cent Saturation of iron binding protein with iron was 35 $\pm$ 6 4 per cent In 13 patients with chronic infections in two dogs in which sterile abscesses were produced and in a single dog with an acute infection TIBC of serum was below normal as was serum iron level Reduction in serum iron value was proportionately greater with the result that per cent saturation with iron was decreased TIBC of serum in six patients with iron deficiency anemia was increased in all Since serum iron level is very low in iron deficiency per cent saturation of iron binding component was below 10 in each instance

Intravenous administration of iron binding globulin (fraction IV 7 of plasma) to two patients with chronic infections increased TIBC of serum to nearly normal for about 24 hours but did not diminish rate of disappearance of intravenously injected iron from serum Furthermore the temporary increase in iron binding capacity of serum did not result in detectable mobilization of iron into the blood Administration of typhoid vaccine to one patient produced transient hypoferremia without significant change in iron binding capacity of serum

From these observations it would appear that some factor other than reduction in iron binding protein is responsible for the hypoferremia associated with infection

Anemia in Hypothyroidism is discussed by Sidney E Eisenberg[8] (Yale Univ) Three types of anemia accompany hypothyroidism The first is the hyperchromic uncomplicated anemia of myxedema with macrocytosis normal color index and normal amount of poikilocytosis and anisocytosis Red cell count is rarely lower than 3 500 000 Reticulocyte count may be normal or a little above Serum bilirubin is normal and cell fragility is slightly increased There may or may not be free hydrochloric acid in the stomach Administration of liver and iron have no effect but the anemia disappears in three to nine months of thyroid therapy

(8) C t cut S t M J 12 11 11 5 D mb 1948

age duration of illness in idiopathic cases was 32/12 months In general the idiopathic cases resembled the tuberculous cases hematologically but the latter group ran a septic course and terminated fatally within a shorter time

Diagnosis of myelofibrosis must be considered when a patient complaining of bizarre pain weakness and weight loss is found to have splenomegaly hepatomegaly lymphadenopathy and hematologic findings of refractory anemia with a leukemoid reaction Tuberculous involvement is to be thought of if there is in addition a recurrent spiking or persistent unexplained fever Bone marrow biopsy must be obtained to confirm diagnosis of myelofibrosis Lymph node biopsies and splenic punctures may be helpful These tissues should be cultured inoculated into guinea pigs and examined histologically for acid fast organisms

Chemical, Clinical and Immunologic Studies on Products of Human Plasma Fractionation Anemia of Infection, Studies on Iron Binding Capacity of Serum It has long been recognized that iron in serum is probably protein bound and recent work has shown that it is bound to both albumin and globulin alpha and beta globulins serving as principal carriers Studies dealing with pathogenesis of anemia of infection have revealed that in the presence of infection iron metabolism is disturbed There is pronounced and persistent hypoferremia increase in plasma iron after intravenous injection of iron is less than in normal persons, and such injected iron disappears from plasma faster than in normal persons In view of these observations it was thought desirable to investigate the role of iron binding protein of serum in pathogenesis of anemia of infection G E Cartwright and M M Wintrobe[7] (Univ of Utah) describe in vitro and in vivo studies of iron binding capacity of serum in normal subjects in patients with infection and in animals in which infections were produced

Total iron binding capacity (TIBC) of serum was

(7) J Clin Investigation 28 86 98 J y 19

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(7) J Clin I est gat on 3 86-98 J u (? 194

and 131 including parents and siblings had the trait for or a mild type of this disease The last figure demonstrates the frequency of the mild form Susceptible population in this country consists of over 5 000 000 persons of Mediterranean origin and the results of the present study indicate that the disease in mild form is probably prevalent where persons of Mediterranean extraction live

Whereas advanced forms of Mediterranean anemia are readily diagnosed milder forms are usually overlooked Importance of detecting asymptomatic persons who bear the trait for the disease is that they constitute a potential source of hereditary transmission of the disease in any of its clinical forms This anemia is of concern to the internist as well as to the pediatrician since the adult not only serves as a carrier but may also have a moderate form of the disease which is frequently incorrectly diagnosed and treated

Whereas the roentgen changes and striking clinical manifestations that characterize the severe form of Cooley s anemia are lacking in persons with the mild form of the disease changes in the blood are distinctive and readily demonstrable Determination of hemoglobin content red cell count measurement of packed red cell volume fragility test and examination of the blood smear constitute essential laboratory procedures Smith s study confirmed the observation that measurement of packed red cell volume constitutes the most accurate single laboratory procedure for diagnosis and therapy in Mediterranean anemia It has been repeatedly shown that red cell count may be misleading in this disease because of the cells striking thinness and alterations in their size so that total count may approach normal despite a considerable reduction in hematocrit value Criteria for diagnosis of mild Mediterranean anemia are as follows (1) Patients are usually of Mediterranean origin principally Greek and Italian (2) They are asymptomatic and may or may not have a mild anemia (3) Blood smear and blood counts show hypochromic macrocytes basophilic stippling oval and target cell and polycythemia (4)

The second type is hypochromic and is the result of myxedema complicated by iron deficiency Administration of iron converts the anemia to the simple hyperchromic or first type

The third type is addisonian pernicious anemia modified by coexisting myxedema Treatment with liver alone converts the anemia to the simple hyperchromic type Blood picture resembles that of uncomplicated pernicious anemia but color index is often higher Serum bilirubin is usually raised Gastric achlorhydria is present The anemia responds rapidly to combined therapy with thyroid and liver

A case of true uncomplicated anemia of myxedema is reported

Woman 43 was referred because of persistent anemia and hypothyroidism Menses had become profuse eight years previously and a severe anemia at that time was attributed to vaginal bleeding The anemia did not respond to iron therapy Thyroid medication for three months and subsequent administration of liver by weekly injection and iron plus liver by mouth for five years also failed and menses remained profuse Examination showed typical findings of myxedema Basal metabolic rate was -40 per cent Gastric analysis revealed free hydrochloric acid Anemia was macrocytic and hyperchromic Thyroid was begun in doses of ½ gr /day and increased over three months to a daily dose of 3 gr At the end of this period basal metabolic rate was -7 per cent Menses had become shorter and less profuse and clinical improvement was striking Therapeutic trial of ferrous sulfate and folic acid for three months had no effect After seven months of treatment with thyroid extract hemoglobin has risen from 10 3 to 11 2 Gm and red blood cells from 3 200 000 to 3 800 000 This slow response to treatment is characteristic of this type of anemia

The following article refers to an important differential diagnosis which may explain the reputed failure of some patients to respond to oral administration of iron —Eds

Detection of Mild Types of Mediterranean (Cooley s) Anemia is described by Carl H Smith[9] (Cornell Univ) on the basis of changes in the blood in 47 families with Mediterranean anemia Blood of 181 persons was analyzed of whom 27 all children were severely anemic

(9) Am J D Child 75 505 5 7 Ap 1 1948

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Morphologic changes in erythrocytes are far in excess of degree of anemia Resistance of red cells to hemolysis in hypotonic solutions of sodium chloride is increased (5) Iron or other forms of antianemia therapy fail to restore normal blood levels (6) One of the more important diagnostic features is the occurrence of similar qualitative alterations in blood of healthy members of the family Analysis of the 47 families in this study revealed that in every instance in which an affected child was recognized similar abnormalities of the blood were discovered in at least one parent In every family with a severely anemic child both parents bore the trait for the disease

[Splenectomy is not generally regarded as useful in the severe form of Cooley s anemia which as stated above appears in the offspring of persons carrying the trait The utility of splenectomy should be measured in terms of hemoglobin increase since an increase of red cells without a rise in hemoglobin is without benefit in terms of blood oxygen transport Perhaps the operation should receive further careful trial —Eds]

Effects of Splenectomy on Cooley s Disease Ignazio Gatto[1] (Univ of Palermo) observed three patients aged 18 12 and 12 respectively for 18 26 months after operation In the peripheral blood he found an increase in red cells to normal or nearly normal values and increase in hemoglobin but with almost invariable persistence of the hypochromasia Thus in the first patient the hemoglobin before splenectomy ranged from 31 to 52 per cent and after splenectomy from 50 to 65 per cent The corresponding ranges for red cells were 2 120 000 3 630 000 before and 3 080 000 to eventually 4 900 000 after In the third patient the effects were more striking hemoglobin ranged from 30 to 42 per cent before splenectomy after splenectomy the highest value recorded was 80 per cent Corresponding red cell values were 3 090 000-3 740 000 before splenectomy and 4 300 000 5 250 000 after

The marked erythroblastosis and reticulocytosis continued increase in average red cell diameter and in maximal cell resistance were followed by decrease in

(1) H m t l g a 31 6 3 671 1949

minimal resistance persistence of the changes in the biophysical characteristic of the red cells increase in number of target cells appearance of some round and hyperchromic cells and marked increase in platelets The bone marrow showed a higher granuloerythroblastic rate which however remained below normal increase in granuloblastic and erythroblastic maturation rate the latter reaching normal increase of lymphoid cells striking decrease of prepolykaryocytes and some change in number of megakaryocytes with prevalence of the more mature elements Other findings included evident reduction in hemolysis disappearance of febrile episodes resumption of body growth with tendency to normalization of its proportions (reduction of Manouvrier s index) resumption of sexual evolution increase in weight improvement in general condition healing of malleolar ulcers reduction of cardiomegaly (one patient) temporarily increased hepatomegaly and no evidence of change in the osteoporosis

The persistence of abnormal erythropoiesis justifies the assumption that the disturbance of the blood status in Cooley s disease must be referred to primary alteration of hemopoiesis Resumption of growth and sexual development after splenectomy suggests that the underdevelopment is due to the noxious action of the splenomegaly to which may also be attributed the appearance of malleolar ulcers

Adult Gaucher s Disease with Special Reference to Variations in Its Clinical Course and Value of Sternal Puncture as an Aid to Its Diagnosis Gaucher s disease is a rare often familial disease distinguished by presence of characteristic cells in organs of the reticuloendothelial system Clinical observations of diagnostic value are idiopathic enlargement of liver and spleen without leukemia a hypochromic anemia with leukopenia and thrombopenia Yellow pigmentation on face and conjunctivas and pigmentation of the lower legs are helpful diagnostic points as are x ray findings of an accumulation of Gaucher cells in bone which ultimately produce

established by detection of Gaucher cells in sternal marrow smears For this purpose thin films should be made and Gaucher cells should be looked for at the end of the smear Smears are stained with the May Grunwald Giemsa stain and examined with low power lens without oil immersion Typical cells will catch the eye at once by their unusual size usually 30-40 μ Cells possess one or two nuclei usually situated eccentrically Nuclei are relatively small with a well stained nuclear membrane and often contain a nucleolus They resemble nuclei of those bone marrow cells sometimes called reticulum or stem cells which are found in small numbers in normal bone marrow An increased number of such reticulum cells may be found in marrow smears of patients with Gaucher s disease Even more common are cell somewhat intermediate in type between the reticulum and Gaucher cell These are probably reticulum cells that have taken up less kerasin and therefore have not changed in type as completely as the typical Gaucher cell They might be called early Gaucher cells

Cytoplasm of the Gaucher cell occupies by far the larger part of the cell body and stains slightly gray or bluish In typical cells it shows a coarse mesh that gives the appearance of compressed tissue paper (Fig 78) Sometimes the cytoplasm contains vacuoles so that it resembles foam cells

Gaucher cells are found in marrow even when no gross lesions seem to be present in bones on x ray Indeed sternal puncture might be called the only method which will enable the clinician to establish with certainty a positive diagnosis of Gaucher s disease It is particularly valuable before the clinical picture is fully developed

Splenectomy with Special Reference to Indications Examination of 45 Splenectomized Patients In an attempt to clarify the indications for splenectomy H Abrahamsen and N B Krarup[3] (Copenhagen) reviewed the histories and re examined when pos ible the 45 patients splenectomized in 20 years at the Bispebjerg

(3 S d (pp 213) 131 9 37 1948

Hospital Of 16 patients operated on with a primary diagnosis of Banti s disease one could not be located for re examination and only 4 of the others were alive Three of the four had improved after splenectomy in one condition was unchanged Four patients had died immediately after operation and the other seven had died in 3 months to 2½ years Revision of diagnoses based on autopsy findings and re examination revealed six cases of liver cirrhosis of such nature that splenectomy was ineffective In three or possibly four cases the diagnosis was thrombosis of splenic veins or hypersplenism with little or no liver cirrhosis three of these patients improved materially after splenectomy and one died of postoperative complications Five cases were of *miscellaneous disorders in which splenectomy* had no effect or was harmful (endocarditis lenta cancer leukosis syphilis and retardation of unknown cause)

Results of this diagnostic revision suggest that the diagnosis Banti s disease should not be used clinically since it tends to obscure important differential diagnostic problems and thus confuses indications for splenectomy In instances of splenomegaly the primary task is to find out whether there is any underlying specific disorder such as leukosis lymphogranulomatosis reticuloendotheliosis Gaucher s disease syphilis tuberculosis etc If so splenectomy is almost always contraindicated [We would except Gaucher s disease since early splenectomy is said to abort further progress and in anemia patients with leukopenia is often useful —Eds] Next the presence of liver cirrhosis and its nature and degree should be determined Again cirrhosis practically contraindicates splenectomy [But with the development of splenorenal vein anastomoses or portocaval anastomoses there is greater possibility of benefit from surgery in patients with cirrhosis —Eds] Splenectomy is definitely indicated in cases of *thrombosis of the splenic vein though diagnosis* is difficult [except at laparotomy —Eds] In cryptogenic hypersplenism splenectomy may result in striking improvement

Of the 12 patients operated on for hemolytic jaundice the disease was of hereditary type in 6 Two patients died immediately after operation but results were good in all others

The immediate result of splenectomy was good in six cases of essential thrombocytopenia although one patient died later of hematemesis In four patients indication for splenectomy was splenic enlargement in three (one with Gaucher's disease one with malaria and one with calcified splenic cyst) results were good In one patient with Pick's disease the result was poor Five of seven patients operated on for traumatic rupture of the spleen recovered

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POLYCYTHEMIA

Polycythemia occurs transiently due to hemoconcentration or chronically in response to arterial oxygen unsaturation a result of the passage of unoxygenated venous blood into the systemic arteries This oxygen deficiency in arterial blood may result from residence at high altitudes or from chronic lung or heart disease In polycythemia vera although arterial oxygen unsaturation does not exist it is theoretically possible that local conditions in the bone marrow create anoxia for the erythropoietic cells This is investigated in the first of the two articles in this section —Ed

Oxygen Saturation of Sternal Marrow Blood with Special Reference to Pathogenesis of Polycythemia Vera An explanation of polycythemia vera has been sought in local anoxia of the bone marrow produced either by local vascular changes or by hyperplastic or neoplastic invasion and consequent mechanical interference with its internal vascular supply Such local hypercellularity may also competitively deprive the erythropoietic cells of oxygen and also stimulate erythropoiesis Lionel Berk Joseph H Burchenal Theo Wood and William B Castle[4] in two series of investigations studied the percentage oxygen saturation of blood removed from the sternal marrow by needle puncture In the first slight suction was used in obtaining the sample and the oxygen content

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(4) Soc Exper Biol & Med 69 316-320 November 1948

and capacity of the sample were determined in duplicate by the Van Slyke manometric combined method In the second no suction was used oxygen content was determined by a modification of the Roughton and Scholander method using only 0 04 ml of blood for each analysis and oxygen capacity was determined with the Evelyn photoelectric colorimeter using a factor of 2 58

Normal subjects convalescent patients without anemia and patients with polycythemia vera secondary polycythemia chronic anemias of various types leukemia or myeloid metaplasia were studied In general no significant differences from the normal were demonstrated except in patients with secondary polycythemia in whom the percentage oxygen saturation of the blood removed from the bone marrow was relatively reduced presumably a result of the manifest unsaturation of arterial blood However in some patients with leukemia and with myeloid metaplasia and in some with polycythemia vera the data suggest an increased local oxygen utilization relative to the blood flow in the bone marrow Thus in the first study the mean oxygen saturation for 21 normal or convalescent controls was $81\ 1 \pm 3\ 49$ per cent In 6 patients with polycythemia vera with normal peripheral white cell counts it was $80\ 4 \pm 1\ 64$ per cent in 7 with polycythemia vera and elevated white cell counts in peripheral blood it was $75\ 0 \pm 2\ 69$ per cent and in 11 anemic patients the corresponding mean value was $81\ 3 \pm 6\ 34$ per cent

Because however even in patients with chronic anemia significant unsaturation was not demonstrated the oxygen contents invariably lying between those of the arterial and of a peripheral venous sample the authors concluded that the technics were not adequate The insurmountable difficulty appeared to be to obtain blood samples satisfactorily representative of the undisturbed environment of the erythropoietic cells of the bone marrow

[The largely negative results of this investigation resemble those obtained by a similar technic in experimental animals by Grant (see this YEAR BOOK p 319) Ed]

Evaluation of Present Forms of Treatment of Polycythemia Rubra Vera Leon O Jacobson and Taylor R Smith[5] (Univ of Chicago) note that primary polycythemia vera characterized classically by ruddy cyanosis polycythemia and splenomegaly must be distinguished from the secondary form which may result from conditions such as congenital heart disease and pulmonary disease with defective oxygenation of arterial blood since certain methods used in treatment of primary polycythemia are definitely contraindicated in most cases of the secondary form For example phenylhydrazine spray radiation and radiophosphorus are of no value in the secondary form whereas repeated venesection may be of definite benefit

Phenylhydrazine acts by producing hemolysis of erythrocytes It has the disadvantages that severe anemia may result from overdosage and that initial administration may precipitate thrombosis Since more effective and less dangerous forms of treatment are available phenylhydrazine is not the treatment of choice

Repeated phlebotomies in amounts of 400 500 cc daily or on alternate days until hematocrit reading reaches 50 per cent may result in maintenance of reduced blood volume and hematocrit level for three to nine months Combinations of venesections with iron free or low iron diets materially reduce number of venesections required to maintain normal blood values [It is doubtful whether a low iron diet is necessary in practice —Eds]

Fowler s solution presumably acts by suppressing erythropoiesis Its disadvantages are that toxicity often occurs there is danger of arsenical poisoning and the drug alone is usually ineffective

Spray radiation given either by total body exposure or by exposing various parts of the body on succeeding days so that eventually most bones concerned in erythropoiesis are irradiated has produced remissions of from six months to over two years Nitrogen mustards used in 10 cases thus far have produced hematologic and

(5) Am P t 3 267 2 0 J y 1949

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constantly involved all tissues except bone which lymphocytes were virtually absent

More specific changes were invariably n l phoid tissue The abnormal lymphocyte cha the disease was 12 15 μ in diameter and wa when distorted by crowding Its cytopla m w l geneous and faintly acidophil The nucleu w delineated Mottled appearance of chromatin w c teristic Indentation and folding of nuclei w re it was impossible to determine if a true nu l present These cells appeared to be atypical l lymphocytes related to or identical with th peripheral blood

Lymph node reactions varied from l follicular hyperplasia to a blurred pattern n malignant lymphoma The pattern was due t n l cytic and reticuloendothelial proliferation in m ular cords Lymphocytic infiltration of the thinne l ca ul and trabeculae of the spleen frequently ren l red the or gan liable to rupture In most instance the pattern in the spleen was partially effaced and follicles were widely spaced Blood sinuses contained many normal and ab normal lymphocytes and accumulation of these cell were found around arteries and beneath intima of vein Lymphocytic proliferation of tonsils was often compli cated by ulceration necrosis and in one in tan e mulated a malignant tumor

One patient had a pneumonic exudate t r und cell type and another pneumonia of the usual lobular type with neutrophilic exudate The small myocar lial infil trates noted probably explain electrocardiographic changes described in infectious mononucleo is Other findings of interest were periportal lymphoid collars in the liver sometimes of the proportions seen in leukemia and meningoencephalitis in four of six brains examined

The authors believe that most of these lymphocytic infiltrates of connective tissue and the perivascular col lars are formed in situ from cells of the reticuloendo thelial system

symptomatic remissions of from 6 months to 2½ years

Remissions produced by radioactive phosphorus appear in general to be longer and more complete than with any other form of treatment Usually 5 7 mc is given initially and repeated in three to six months if remission has not been produced Venesections may be performed before phosphorus injection to alleviate symptoms and to reduce danger of thrombosis during the period in which the radiophosphorus is exerting its effect If incidence of leukemia especially of acute leukemia is not increased by radiophosphorus it may prove to be the treatment of choice

[Since in our opinion polycythemia vera is in many instances a response to the presence of early leukemic infiltration of the bone marrow it is likely that leukemia will develop in many of these patients irrespective of the method of treatment—Ed]

LEUKOCYTOSIS AND LEUKOPENIA

The articles in this section describe various aspects of infectious mononucleosis and of neutropenia associated with splenomegaly The first article describes much of the available knowledge derived from autopsies of nine fatal cases of infectious mononucleosis—a condition usually assumed to be entirely a self limited and benign disease—Ed

Pathology of Infectious Mononucleosis R Philip Custer and Edward B Smith[6] studied sections from nine autopsies and many biopsy specimens chiefly of lymph nodes and bone marrow of patients with infectious mononucleosis Gross changes were almost exclusively confined to enlargement of lymphoid tissue especially spleen Nasopharyngeal lymphoid hyperplasia was constant and in one instance suggested tumor There were no significant gross features in other tissues which could be related to the primary disease except liver enlargement infrequent icterus and occasional skin rashes Histologic sections showed perivascular aggregates of normal and abnormal lymphocytes of a type resembling that seen in certain virus diseases Changes of this type in

(6) Blood 3 830 857 Aug t 1948

struction of the common duct by enlarged lymph nodes

[This article should be read in th original by those who desire a careful review of the pertinent literature

The next article call attention to an asp ct of infectious mononucleosis which is important to anti ipate e pecially in the manag ment of younger and more active patient —Ed]

Splenic Rupture in Infectious Mononucleosis Joseph J Timmes James H Averill and James Metcalfe[8] (Newport R I) report two cases

Case 1—Youth 19 was hospitalized because of left upper quadrant pain for two days after having been struck a light blow in the epigastrium One month before he had had swollen cervical lymph nodes and fever with malaise and anorexia His red cell count was 3 400 000 with 9 5 Gm hemoglobin Laparotomy was performed immediately and an enlarged spleen with a hematoma on its lateral surface removed Four days later heterophil antibo ly agglutination was positive in dilutions up to 1 1 792 Histologic appearance of the spleen was compatible with but not diagnostic of infectious mononucleosis

Case 2—Youth 19 was hospitalized for nausea and vomiting of 4 days duration and abdominal pain for 24 hours One week before he had had coryza sore throat cough and malaise Abdominal pain was generalized but at the onset had been in the left upper quadrant Examination revealed a questionable left upper quadrant mass Heterophil antibody agglutination was positive in dilutions up to 1 3 584 Laparotomy was performed and an enlarged lacerated sple n removed The pathologic diagnosis was acute splenitis and infectious mononucleosis

Fourteen cases of rupture of the spleen in infectious mononucleosis have been reported The authors suspect that this condition is more common than has been recognized They suggest diagnostic tests for infectious mononucleosis in patients suspected of splenic rupture To prevent this complication heavy exertion should be avoided for 14 30 days after onset of infectious mononucleosis because all but one of the reported instances of splenic rupture in infectious mononucleosis occurred during this period Repeated palpation of the enlarged spleen should also be avoided Patients with infectious mononucleosis should be observed carefully for evidences of splenic rupture

[Because the d agnosis of splenic neutropen a apparently rests on

(8) N w E gl d J M d 39 173 175 J ly 9 1948

That the authors were able to study material from 9 autopsies and to record 12 additional deaths from the disease indicates that infectious mononucleosis is not always benign

Hepatic Dysfunction in Infectious Mononucleosis With Review of Literature Ralph E Peterson (Univ of Minnesota) studied 40 consecutive patients with unequivocal infectious mononucleosis for evidence of liver dysfunction Liver function tests used were the one minute and total bilirubin thymol turbidity thymol flocculation cephalin cholesterol flocculation bromsulfalein (5 mg 45 minute) alkaline phosphatase total cholesterol and cholesterol esters urinary Ehrlich reaction and urinary coproporphyrin

In over half the patients tested the alkaline phosphatase bromsulfalein urobilinogen and urinary coproporphyrin tests gave positive results Of the 40 patients 21 had clearcut signs of impaired hepatic function evidenced by three or more liver function tests exclusive of the test for urinary coproporphyrin A few of the remaining 19 patients showed questionable evidence of hepatic dysfunction on the basis of one or two mildly positive test *results*

Only one of the patients with impaired hepatic function had definite jaundice and only four had an enlarged liver About half of patients with and without evidence of hepatic dysfunction had splenomegaly None had serious complications Liver function tests showed a return to normal in a short time

In differentiating infectious mononucleosis with hepatic dysfunction from acute epidemic or sporadic hepatitis reliance must be placed on the clinical picture especially the presence of pharyngitis type of lymphocytic reaction and titer of heterophil antibodies Character of the liver function disturbances in patients with infectious mononucleosis points to both hepatocellular and cholangiolar liver injury Results of the study tend to refute the theory that the jaundice is due to extrahepatic ob

(7) J Lab & Cl Med. 33 1 58 1 70 O

liver and vitamin therapy are helpful but the only treatment of definitive value is splenectomy As soon as this is done there is increase in polymorphonuclear leukocytes in the blood similar to the increase in platelets after splenectomy in thrombocytopenic purpura There may even be temporary overproduction of white cell at levels of 20 000-30 000 but this soon diminishes The young forms di appear from the blood and the anemia di appears In two patients the disorder di appeared after operation in a third size of the spleen was reduced by radiotherapy In a fourth with malaria quinacrine treatment caused reduction in size of the spleen and doubling of the neutrophils in the blood

Histologically the spleen shows diffuse proliferation of the reticuloendothelial system and generalized fibrosis Accumulations of myeloid and macrophagic cells are visible

Mallarme considers the syndrome to be due to a restraining action of the spleen on leukocyte formation in the bone marrow Similar hypotheses have been proposed for certain splenic anemias and for thrombopenia The mechanism of the inhibiting action is not clear

Case of Cyclic Agranulocytosis with Marked Improvement Following Splenectomy is reported by H W Fullerton and H L D Duguid[1] (Univ of Aberdeen) Cyclic agranulocytosis has been reported in seven patients In five the condition started in infancy and was characterized by complete or almost complete disappearance of neutrophils from peripheral blood at regular intervals of about 21 days Pyrexia and ulceration of the mouth were main features of the attack Agranulocytosi recurring with menstruation was excluded from consideration because of the possibility that patients had taken drug (e g amidopyrine) at on et of menstruation The authors patient i unique in that he is a man in whom cyclic agranulocytosis developed in advanced adult life and because splenectomy greatly modified the recurrent agranulocytosi

(1) Blood 4 9 M h 1949

exclusion of the possibility of other recognizable conditions in any patient with splenomegaly and neutropenia further information of any kind is useful However so long as these characteristics are common to such conditions as aleukemic leukemia myeloid metaplasia and refractory anemia with cellular bone marrow—none of which can be diagnosed with complete certainty at any one stage of development—the chances of permanent relief by splenectomy are difficult to evaluate in advance Fullerton and Duguid in the second article following present tangible evidence that cyclic neutropenia resulted from changes of the myeloid function of the bone marrow —Eds]

Neutropenic Splenomegaly is a rare condition which J Mallarme[9] (Paris) has seen in four patients all adults three of whom were women Complaints were of fatigue digestive upsets and soreness of the mouth or pharynx The symptoms occurred in attacks during one of which examination disclosed a large spleen The splenic enlargement was similar to that in Banti s syndrome the spleen being hard regular mobile and tender during attacks With enlargement there was fever weight loss and marked asthenia Liver and lymph nodes were not enlarged there was no ascites icterus or clinical or laboratory signs of increased hemolysis

Study of the peripheral blood showed marked neutropenia (1 500 6 000 leukocytes) amounting to 10 20 per cent of the white cell count The granulocytes were adult neutrophils or occasionally band forms and even myelocytes and metamyelocytes There was some relative increase in eosinophils Red cell count varied between 3 500 000 and 4 500 000 being lower during attacks Some deficit in platelets increase in capillary fragility and prolongation of bleeding time were found at times Marrow studies indicated in general normal active hemopoiesis at times there were signs of mild hypo or hyperplasia The splenogram was of a lymphomonocytic type with some large splenocytes and macrophages In two patients there was also a myeloid reaction like that in the blood

When untreated the disease develops in attacks with increase in symptoms Infections of mouth and skin occur with the bouts of neutropenia Rest transfusions and

(9) Arch mal l 1 109 1 5 1948

LEUKEMIAS AND RELATED DISORDERS

The number of articles in this section dealing with the chemo therapy of leukemia and lymphomas testifies to the present and widespread interest in this subject However in harp contrast to the implications of the num rous press and rad o report none of the currently used chemotherapeutic agents promises a great ad vance in treatment. Thus except for the effect of nitrogen mustard on the later stages of Hodgkin s disease and perhaps of urethane in multiple myeloma it is difficult to be convinced that results are as useful as those obtained with accepted forms of x ray irradiation Readily available blood and control of secondary infection by mod ern antibiotics are important adjuvants of all forms of treatment especially in the management of acute leukemias in which the ef fects of analogues of pteroylglutamic acid are being actively studied In th s d fficult field it is probably a sound policy to rely on methods with which the physician is per onally familiar than to conclude that what is new mu t neces arily be bett r

The first two article re examine earlier reports by other authors that urinary extracts from patients with leukemia cause hyperplastic myeloid or lymphoid responses in the hemopoietic tissues of guinea pigs Because urinary extract from most persons as well as ex tracts of normal animal tissues produce similar effects a significant relation of the observations to the genesis of leukemi i seems d ubt ful Moreover it is well known that in animals the presence of necrotic tumors or the injection of nucleic ac d may produce sim lar myeloid hyperplasia In man tumor necrosis may cau e a leukemoid reaction in which the white cells in periph ral blood may go above 100 000/cu mm The e responses are not however regarded as leukemic —Ed

Effects of Hepatic and Splenic Extracts from Human Lymphomas on Lymphatic System of Experimental Ani mals It has been postulated that leukemia and Hodgkin s disease are produced by specific lymphoid and myeloid stimulating substances which can be isolated from urine feces liver and spleen of human subjects with leukemia or Hodgkin s disease and from normal beef liver Changes interpreted as those of leukemia or Hodgkin s disease have been found in animals given injection of these substances Furth pointed out that no information exists as to whether these substances are by products of the growth of lymphocytic and myelopoietic tissues or cause diseases of these tissues

John B Storer and Clarence C Lushbaugh (Univ

( ) C R h 9 109 113 F b ry 1949

Man 62 was hospitalized June 6 1946 because of recurrent sore throats since October 1945 During one attack he had also had boils Sulfadiazine had been given during each attack. During the first nine months in which the patient was studied he had 12 attacks of agranulocytosis lasting 4 5 days at inter vals of 23 28 days With each attack he had malaise anorexia drowsiness headache pyrexia and various infections In each attack throat and tonsils were inflamed Mental depression became more severe with each attack As granulocytes reap peared fever and infection subsided and well being quickly re turned Throughout the nine months red cell count remained around 4 000 000 hemoglobin value 80 per cent and platelet count 100 000 350 000

To determine whether the agranulocytosis was the result of failure of marrow production or of excessive destruction in peripheral blood eight marrow aspirations were done at inter vals of a few days throughout one typical cycle Appearance of neutrophils in peripheral blood was preceded by rise first of myeloblasts then of premyelocytes and finally of myelocytes in marrow and diminution of granulocytes in peripheral blood was presaged by diminution of early myeloid cells in marrow It was concluded that the agranulocytosis resulted from pe riodic failure of marrow to produce neutrophils

Adrenalin 1 cc subcutaneously precipitated increase in peripheral neutrophils when given between attacks of agranulo cytosis but not wh n given during an attack To discover if the *patient s plasma contained a substance capable* of depressing leukopoiesis a pint of his blood was twice given to another sub ject the recipient s leukocytes were not affected

Penicillin was given with each attack Pentnucleotide® given with the first attack was discontinued because it produced un desirable reactions and had no clearcut favorable effect Neither benadryl® nor lertigon® had any effect on the poly morphonuclear curve Pyridoxine and sulfadiazine likewise were without effect

Without very rational foundation splenectomy was proposed and performed Spleen was three or four times normal size but was otherwise grossly and microscopically normal Leuko cytosis occurred promptly and reached a maximum of 18 900 with 83 per cent neutrophils five days after operation There after white cells fell rapidly but neutrophil count fell only to 406/cu mm and then began to rise again A month later neutrophil count fell to 90/cu mm but thereafter although fluctuations occurred lowest neutrophil count was 640/cu mm The patient s health improved greatly and when seen two years after splenectomy the leukocyte count was 8 500 of which 47 per cent were neutrophils He had had no infection

this experiment was too small for statistical significance similarity between the ages at death from leukemia age ranges and total incidence of leukemia in the two groups indicated that injection of the extracts had no effect on the incidence of leukemia or the leukemic disease of these mice

Lymphocytic infiltrations comparable to those illustrated in previously published reports were found in both control and experimental animals but such infiltrates are common in healthy young guinea pigs and result from a wide variety of nonspecific stimuli such as mild laboratory infections and injections of foreign substances

Observations in Guinea Pigs Following Injection of Specific Hemopoietic Substances Derived from Urines of Human Leukemic Subjects are reported by Arthur Sawitsky and Leo M Meyer[3] (New York Univ) Urine of patients with proved myeloid or lymphoid leukemia were collected pooled extracted and then injected into guinea pigs Several methods of extraction were used

Animals into which the urine extracts were injected became ill Ruffled fur lethargy and stertorous respiration were common Hindfeet became ulcerated after the larger doses The peripheral blood picture was altered only in occasional animals in which severe anemia developed and normoblasts and occasional myelocytes appeared in the peripheral blood

Autopsy showed that animals given urine from patients with lymphoid leukemia had lymphoid leukemia like lesions Animals given urine from patients with myeloid leukemia showed lesions resembling those of myeloid leukemia Substances in which urine extracts were suspended did not produce similar changes

Lesions produced by the lymphoid fractions were most frequent in lymph nodes liver lung kidney and bone marrow Animals stimulated by myeloid fractions most often showed lesions in the spleen bone marrow liver lymph nodes and adrenal cortex There was no difficulty in identifying and removing the thymus of animals given

(3) Am J P th 24 1117 1135 S p mt 1948

of Chicago) repeated experiments on which these conclusions are based and were unable to substantiate the findings reported. Extracts were made from livers and spleen of 11 patients who died of various lymphomas. The same organs of one patient with erythroblastic anemia and one with sympathoblastoma were extracted to use as controls. Methods were similar to those described by the original investigators.

The organ extracts were injected subcutaneously into 37 guinea pigs. Only one animal died during the month after injection and autopsy of the others 28-32 days after injection showed no abnormality. For controls four untreated guinea pigs were killed. Sections were made of liver, spleen, lymph nodes, thymus, lungs, adrenals, kidneys and bone marrow of all animals. No evidence of definite specific lymphocytic stimulation could be found in any animal. Lungs could not be used in this assay because most of the animals, regardless of previous treatment, showed large nodular infiltrates of mature and immature lymphocytes around pulmonary blood vessels. Many untreated animals showed more extensive infiltrates than did treated ones.

In the next experiment 24 mice of a strain especially susceptible to lymphoid leukemia were given injections of the organ extracts. They were killed 29-39 days after injection and studied histologically for evidence of leukemoid changes or lymphocytic infiltrations. Another 20 mice served as controls. None of the organs of the animals given the injections showed lymphocytic infiltrate in excess of the minute foci normal in these animals.

In the third experiment 100 mice of the same lymphoid leukemia sensitive strain received injections. Though many died because of the acute toxicity of the extracts and because of the fighting habit of this particular strain, 47 mice survived over 180 days. Of the 87 mice adequately studied at autopsy none died of leukemia less than 180 days after injection. Average age at time of death from leukemia was about the same as that of 86 control mice of the same strain. Though the number

teum etc There is however no correlation between extent of the leukemic bone changes and subjective osteoarticular symptoms In two cases reported by Bichel bone changes were slight but symptoms so severe that rheumatic fever was diagnosed In a third case there were no subjective symptoms from the bones and joints



Fig 79—A t po t d lat l film f k f l k m boy g d 15 m th (Cou t y f B h l J A t b m l 1 153 164 1948)

but the bone changes were severe with a spontaneous fracture (Fig 79)

Joint symptoms in leukemia in children are probably much more frequent than generally believed Bone x rays may permit differential diagnosis especially when the clinical picture suggests rheumatic fever If the examination shows changes compatible with leukemia the conditions to be differentiated are scurvy osteomyelitis and osteitis fibrosa hemolytic and sickle cell anemia neuroblastoma syphilis tuberculosis and rickets

lymphoid fractions but great difficulty in animals given myeloid fractions It was evident that stimulation of myeloid tissue caused reduction of lymphoid tissue and vice versa

It is concluded that urine of patients with leukemia contains substances capable of producing lymphoid or myeloid hyperplasia in guinea pigs Though leukemia like the changes are not leukemia Efforts are being made to purify and concentrate the active fractions from urine of patients with leukemia

The following article emphasizes the need for awareness of the varied early manifestations of leukemia in children —Ed

Arthralgic Leukemia in Children According to Jørgen Bichel[4] (Univ of Aarhus) the course and clinical manifestations of leukemias in childhood and in adult life are different Osteoarticular symptoms are common in children and may dominate the clinical picture whereas they are rare and appear late in leukemias in adults Not infrequently joint symptoms may be the initial symptoms in leukemia in children closely resembling those of acute rheumatic fever High fever and severe joint pain may occur without warning The joint may be inflamed or appear normal The pain often shifts from joint to joint There may be functional systolic cardiac murmurs suggesting endocarditis Sometimes onset is insidious and difficulty in walking progresses to seeming paralysis without neurologic signs Generally no inflammatory changes are found in the joints even at autopsy but in some cases x ray studies or autopsy reveal changes in the metaphyses of the long bones Bone changes are often signs of leukemia in children There may be bone absorption generalized osteoporosis and even spontaneous fractures and gibbus formation Periosteal layering is common and some writers have called attention to a narrow band of diminished density parallel to the epiphyseal lines Osteosclerosis is uncommon The bone changes are attributable to extension of marrow infiltration of bone by leukemic cells lifting of the perios

(4) A ta h m t l 1 153 16.

generally thought that therapy lengthens the period of comfortable and useful life

Though no real explanation of the long duration of leukemia in some patients is apparent it has been claimed that certain findings connote poor prognosis Among these are very high or very low white cell counts severe anemia many blast cells excessively high or low platelet counts marked splenomegaly diffuse lymph node involvement and presence of complications such as hydrothorax pneumonia tuberculosis osteomyelitis and cardiovascular disease It has been thought that long duration of symptoms before diagnosis suggests a more chronic form of the disease

[This article is salutary reading for those attempting to evaluate the effectiveness of chemotherapy in leukemia on the basis of comparative survival times —Eds]

Histopathologic Effects of Nitrogen Mustard Therapy on Normal and Neoplastic Hemopoietic Tissues were studied by Matthew Block Charles L Spurr Leon O Jacobson and Taylor R Smith[6] (Univ of Chicago) The nitrogen mustard compound methyl bis(β chloroethyl) amine hydrochloride was given in standard dosage of 0 1 mg/kg intravenously on four successive days The most satisfactory method of obtaining tissue for biopsy was found to be repeated puncture of the same lymph node (or spleen) by means of a Vim Silverman needle under local anesthesia since this method made possible serial study of the same node

Bone marrow exhibited slight increase in number of degenerating cells 24 hours after any single injection of nitrogen mustard This primary cytotoxic phase was followed by an atrophic phase due primarily to decrease in neutrophil and eosinophil precursors The atrophic bone marrow phase preceded closely the leukopenic phase in peripheral blood About 15 20 days after injection of nitrogen mustard a regeneration phase began Regeneration always took place after a therapeutic dose and in some patients actual hyperplasia occurred

(6) Am J Cl Path 18 6 1 689 Sept mb 1948

Chronic Leukemia of Long Duration With Report of 31 Cases with Duration of over Five Years The records of the 31 patients analyzed by Herbert C Moffitt Jr and John H Lawrence (Berkeley, Calif) yielded no hint as to why certain patients with leukemia survive longer than others

Average survival from time of first symptoms in 16 patients with chronic lymphoid leukemia was 8 16 years and duration of the disease in 15 patients with chronic myeloid leukemia averaged 6 47 years Review of the literature revealed that average survival in myeloid leukemia has been reported to vary from 1 68 to 4 3 years and survival with chronic lymphoid leukemia from 1 07 to 4 33 years A patient with chronic lymphoid leukemia has been reported to have survived 25 years and one with myeloid leukemia 18 years There are several well authenticated cases of chronic leukemia in which apparent cure has occurred [As there is no biologic test for leukemia such as the transplantation of a tumor to the anterior chamber of a rabbit s eye whether or not a patient has leukemia rests on purely morphologic considerations—unless the patient dies of the disease —Eds]

Age at onset is generally agreed to have no bearing on duration of chronic myeloid leukemia whereas some writers believe that chronic lymphoid leukemia is more malignant in persons under 40 while others have come to the opposite conclusion

Spontaneous remissions are said to occur in somewhat less than 10 per cent of patients with both chronic myeloid and chronic lymphoid leukemia Various types of infection have been reported to have precipitated remissions but leukemic manifestations recurred soon after infections disappeared In the great majority of patients infections do not produce remission and in an occasional patient infection causes increase in white blood cell count

There is no conclusive evidence that treatment significantly prolongs the duration of the disease but it is

(5) A I I M d. 30 78 789 Ap l 1949

ence between cancer cells and normal cells The differences found are quantitative Knowledge of a qualitative difference would make feasible a search for chemotherapeutic agents against cancer on a far more rational basis At present this search is somewhat blind and research workers have set out to test innumerable widely different chemical compounds So far no substance with a selective destructive action on malignant cells has been found Almost all the chemotherapeutic agents employed make use of the fact that so called malignant cells are evidently more susceptible to damage than normal cells This susceptibility may in turn be due largely to the fact that the more rapidly cells proliferate the more vulnerable they seem to be

The chemotherapeutic agents now available are toxic substances which in small doses inhibit or destroy rapidly proliferating malignant tissue but in doses large enough to destroy all malignant tissue damage normal tissue to such an extent that survival is impossible The rapidly proliferating cells of blood forming organs especially are damaged by such toxic doses

In hyperplastic processes in hemopoietic tissue chemotherapy has long been known and used Arsenic as Fowler s solution and benzene have been used for many years in leukemia and if properly administered can produce remissions

In estimating the practical value of new chemotherapeutic agents against leukemia their palliative effect and ability to prolong life must be compared with those of radiation the best known treatment

Urethane (H NCOOC H) an ester of carbamic acid causes some regression in leukemic processes presumably through inhibition of mitosis The effect is most pronounced in typical chronic myeloid leukemias less in chronic lymphoid leukemias and absent in acute leukemias In chronic myeloid leukemia leukocyte counts fall hemoglobin and red cells increase and marrow composition is normalized spleen size reduced and general condition improved Such a remission is occasionally as

Lymph nodes in Hodgkin's disease of the paragranulomatous granulomatous type showed slightly increased degeneration involving lymphocytes granulocytes and Sternberg Reed cells but not reticular cells, after nitrogen mustard therapy Results in the sarcomatous type of nodes were less marked correlating with the comparatively short clinical remission achieved

In lymphosarcoma and lymphoid leukemia intense lymphocytic destruction followed nitrogen mustard therapy especially in the nodules in lymphosarcoma and in perivascular areas in lymph nodes in lymphoid leukemia

In far advanced multiple myeloma myeloid leukemia and metastatic carcinoma limited observations failed to demonstrate any significant clinical or histologic change after nitrogen mustard therapy

These studies lend further weight to the experimental demonstration that reticular cells and plasma cells are resistant to the necrotizing effects of nitrogen mustard The principal cytotoxic effect of this drug seems to be on small lymphocytes myelocytes erythroblasts and megakaryocytes Except in nodules in some lymph nodes mitoses were but little inhibited in any cell type seen and in no instance did nitrogen mustard restore to normal the basic architectural pattern of tumor tissue The essential nature of the diseases studied was unaltered It seems probable that therapies of neoplastic diseases of the hemopoietic tissues which rely on destruction of more susceptible cells are doomed to failure because the immature reticular cells in reserve serve as a source of cell regeneration and carry on the malignant properties of the disease

The following article also contains a sound appraisal of the limited possibilities of present attempts at chemotherapy of malignancy in the absence of a qualitative difference between normal and neoplastic cells —Eds

Chemotherapy in Leukemia Hodgkin's Disease and Allied Disorders is discussed by Jørgen Bichel[7] (Univ of Aarhus) Despite an enormous amount of research work it has never been possible to prove any chemical differ

(7) Act d 1 30 49 63 1948

ence between cancer cells and normal cells The differ ences found are quantitative Knowledge of a qualitative difference would make feasible a search for chemotherapeutic agents against cancer on a far more rational basis At present this search is somewhat blind and research workers have set out to test innumerable widely different chemical compounds So far no substance with a selective destructive action on malignant cells has been found Almost all the chemotherapeutic agents employed make use of the fact that so called malignant cells are evidently more susceptible to damage than normal cells This susceptibility may in turn be due largely to the fact that the more rapidly cells proliferate the more vulnerable they seem to be

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pronounced as that following successful radiation therapy However individual remissions due to urethane seem to be of shorter duration than those produced by radiation and side effects are more pronounced Though it is of great theoretical interest that another substance affecting hyperplastic leukemic processes has been found urethane treatment does not seem to constitute any great advance

Nitrogen mustard compounds are alkylamines derived from mustard gas Various workers have reported that these drugs have a definite palliative effect in various hemopoietic neoplasms particularly Hodgkin s disease Affected lymph nodes decrease in size temperature becomes normal itching abates and general condition greatly improves Cure is not claimed Nitrogen mustards are toxic to all cells but their action on rapidly proliferating cells is marked Therefore the aim is to find a dose producing the greatest possible effect on abnormally proliferating cells without simultaneous irreparable damage to the host Remissions in Hodgkin s disease are often brief On the whole they seem much shorter than those obtained by roentgen irradiation and investigators generally agree that nitrogen mustard therapy is not superior to x ray therapy Nitrogen mustard seems indicated for patients resistant to radiation therapy and those with generalized Hodgkin s disease without localized foci easily accessible to radiation

During a search for drugs with trypanocidal effects stilbamidine* was found valuable in treatment of kala azar In kala azar as in multiple myeloma there are changes in protein content of the serum with hyperglobulinemia and on this slender analogy stilbamidine* was tried in myeloma Whereas the drug did not influence the abnormal protein condition it seemed to exert a selective action against the myeloma cell and alleviated symptoms especially pain Cure is not obtained It is too early to predict the practical importance of this treatment

In general the clinical results of the ... othera

peutic agents do not encourage optimism as in most cases other methods offer equally good or better results

Urethane Therapy in Leukemia Adolph J Creskoff Thomas Fitz Hugh Jr and John W Frost[8] (Univ of Pennsylvania) report results of urethane therapy in 24 patients with leukemia Average daily dose was 4 Gm orally Intravenous administration is also practicable

Of seven patients with chronic myeloid leukemia two had satisfactory clinical and hematologic remissions after urethane therapy as did two of seven patients with chronic lymphoid leukemia Though prompt fall in total leukocyte count followed urethane treatment of 10 patients with acute leukemia of various types and evanescent improvement occurred in 4 8 of the 10 died soon after therapy Final information on the other two patients is not available

Nausea was the most prominent symptom of intolerance and occurred in about half the patients The most dangerous toxic manifestation was depression of all marrow elements Rapidly developing anemia calls for immediate cessation of urethane therapy

The authors conclude that urethane is of definite but limited value in chronic leukemia In some instances its results compare favorably with those of x ray therapy but in general it is less dependable particularly in its frequent failure to induce optimal return of normal red cell and platelet values and optimal regression of organ infiltration

Some Observations on Effect of Folic Acid Antagonists on Acute Leukemia and Other Forms of Incurable Cancer The stimulating effect of folic acid on bone marrow suggested to Sidney Farber[9] (Harvard Univ) that folic acid antagonists might inhibit bone marrow and be of use in treatment of leukemia Impressive remissions in acute leukemia were produced first by aminopterin® in doses of 0 5 1 0 mg daily and later by related but less toxic folic acid antagonists amethop

(8) ...d 3 896 910 A gu t 1948
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terin* 3 5 mg daily and amino an fol* 25 50 mg daily Dosage should be determined each day guided by physical findings and white cell count Too rapid drop in white count diarrhea of unknown origin stomatitis soreness of the tongue or ulceration of the mouth warrant cessation of treatment These abnormalities and the finding of megaloblasts in bone marrow suggest that changes in acute leukemia produced by folic acid antagonists are manifestations simply of folic acid deficiency but there is some suggestion that more complicated changes are involved

The longer survival of patients with acute leukemia made possible by folic acid antagonist therapy has centered attention on the problem of hemorrhage Both leukemic infiltration of the intestinal tract and the effects of folic acid antagonists promote gastrointestinal hemorrhage Studies are being conducted to determine if bleeding in patients with acute leukemia is the result of thrombocytopenia or of recently discovered increases in concentration of heparin like substances in the blood or of both

Of 60 children with acute leukemia treated for three weeks or longer with aminopterin* amethopterin* or amino an fol* more than 50 per cent improved clinically and hematologically Though survival beyond the usual course of the disease has occurred in some patients given folic acid antagonists no evidence has been presented which would justify use of the word cure

Folic acid antagonists also effected temporary improvement in patients with neuroblastoma carcinoma of the bladder with pulmonary metastases lymphosarcoma and Hodgkin s disease

Aminopterin* (Folic Acid Antagonist) in Treatment of Leukemia Since the isolation and synthesis of pteroyl glutamic acid in 1946 a number of chemical analogues and homologues having similar or antagonistic biologic activity have been developed and their actions studied It has been reported that Rous sarcoma failed to grow in chicks fed a folic acid deficient diet wh ddition of

this compound produced neoplasm in 100 per cent of animals Inoculated chicks on a balanced diet containing folic acid failed to show any tumor growth when treated with three different folic acid antagonists one of which was 4 amino pteroylglutamic acid (aminopterin®)

A number of investigators have reported temporary clinical and hematologic improvement in patients with acute leukemia treated with folic acid antagonists The present report summarizes a study in which Leo M Meyer Harold Fink Arthur Sawitsky Manuel Rowen and Norton D Ritz[1] (New York Univ) collaborated with several investigators in other institutions Forty three patients with leukemia were given aminopterin ® 18 with acute and 3 with chronic myeloid leukemia and 19 with acute and 3 with chronic lymphoid leukemia

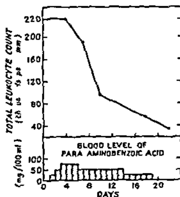
In only four patients did the hematologic and clinical picture improve The four all children with acute leukemia (lymphoid in three myeloid in one) showed reduction of cell count and increased maturity of cell type The other patients showed no change or were adversely affected (in 14 patients moderate to severe leukopenia with hypoplasia of bone marrow developed) Aminopterin® had no significant effect on hemoglobin erythrocytes platelets or temperature of patients with acute leukemia A few patients showed some reduction in size of lymph nodes spleen or liver

Fifteen patients showed toxic effects necessitating discontinuance of treatment Leukopenia with severe irreversible hypoplasia of the marrow was the most serious complication and was most prominent in patients with lymphoblastic leukemia This toxic effect was commonest in patients receiving the drug for the longest periods Total dosage and dosage per body weight could not be related to marrow hypoplasia Mucous membrane lesions were the most frequent and most troublesome toxic signs Ulceration of buccal and pharyngeal mucosa was common Hematemesis and rectal bleeding were believed the result of lesions of gastrointestinal mucosa

(1) Am J Cl P th 19 119 I 6 F bru y 1949

The most striking findings in this study were the unpredictability of action of aminopterin® and its toxicity Neither beneficial nor toxic effects could be controlled or related to dosage of aminopterin® alone or to its administration simultaneously with liver extract or other supportive measures These faults will severely limit the usefulness of aminopterin®

Para aminobenzoic Acid in Leukemia Effect on Leukocyte Count Though leukemia is generally accepted as a neoplastic disease certain tissue culture experiments still hold out the faint hope that the leukemic cell can mature into a normal leukocyte under suitable nutritional conditions To pursue this possibility H B May and J Vallance Owen[2] (London Hosp) used para aminobenzoic acid an essential metabolite for many bacteria in treating five patients with chronic myeloid leukemia, one with chronic lymphoid leukemia and one with acute leukemia All patients received 0 5 Gm /lb body weight/24 hours in divided doses every 2 hours from 6 a m to 10 p m Blood concentrations between 60 and 100 mg /100 ml were obtained after the first 24-48 hours



F g 80 —Le ko yt c t n la t n t blood c t at of p r m ben o ac d n p t e t w th ch c my l d l ukemi (Courte y of May H B nd Vall n Ow J Lan et 2 607 609 Oct 16 1948)

All five patients with chronic myeloid leukemia showed a remarkable drop in total leukocyte count and decrease in spleen size Within 21 days total leukocyte count could be brought within normal limits but on cessation of treatment it rose rapidly to former values (Fig 80) After the count had returned to former values a second course of treatment again produced a rapid fall

(2) L t 2 607-609 Oct. 16 1948

Differential counts of leukocytes in peripheral blood and sternal marrow remained unchanged No drop in count was obtained in the patient with lymphoid leukemia and total leukocyte count rose during treatment of the patient with acute leukemia

Patients general condition was little affected The most serious toxic effect was unexplained hemorrhage which did not appear to be due to deficiency of prothrombin vitamin C or platelets

The effect of para aminobenzoic acid is attributed to the fact that it is a toxic substance with a far higher toxicity for granular cells of the myeloid series than for cells of the lymphoid series or for very primitive hemic cells

Multiple Myeloma Its Clinical and Laboratory Diagnosis with Emphasis on Electrophoretic Abnormalities W S Adams E L Alling and J S Lawrence[3] (Univ of Rochester) reviewed records of 61 patients with multiple myeloma Commonest clinical abnormality present in 98 per cent was pronounced dental caries or complete absence of teeth Possibly these abnormalities result from the same process which causes osteoporosis Of the 61 patients 89 per cent were over 50 the youngest being 31 The disease was 2½ times more frequent in males Sixty eight per cent had pain—either insidious rheumatic bone pain of progressive severity probably related to the osteolytic process or sudden acute pain from pathologic fractures Sixty eight per cent had weight loss which averaged 29 lb Sixty two per cent had gastrointestinal symptoms but these usually were not severe Fifty two per cent had fever usually low grade

Forty seven per cent of patients had pallor with a peculiar dusky sallow color Hemorrhage from nose gums lungs and gastrointestinal tract and into the skin occurred in 39 per cent of patients and profuse hemorrhage followed surgical procedures in three patients This hemorrhagic tendency in multiple myeloma is not understood There is no known defect in clotting mecha

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[3] J M d 6 141 161 F b y 1949

nism It has been suggested that the bleeding tendency is related to hyperproteinemia Neurologic disorders usually resulting from pathologic fractures of vertebrae occurred in 35 per cent Liver was palpable in 26 per cent and spleen in 9 per cent Bone tumors were palpable in 22 per cent

Bence Jones protein was detected in 47 per cent Bence Jones protein may be present only intermittently early in the course of the disease and its detection may be handicapped by presence of albumin or globulin in urine It is sometimes possible to remove albumin by filtration Cloudiness between 45 and 85 degrees C suggests Bence Jones protein Plasma protein concentration was over 8 Gm per cent in 52 per cent of patients and 67 per cent had hyperglobulinemia The euglobulin fraction is usually the one increased in this as in other conditions characterized by hyperglobulinemia Electrophoretic detection of increased amounts of pseudoglobulin I or II by the Tiselius apparatus differentiates the hyperglobulinemia of multiple myeloma from that of other conditions It has previously been shown that when Bence-Jones protein is found in urine hyperglobulinemia is usually absent This observation was confirmed in the authors series Electrophoretic experiments suggest that when serum globulin is increased Bence Jones protein in blood may be attached to this globulin and therefore not excreted in urine Conversely absence of hyperglobulinemia permits excretion of Bence Jones protein in urine

Plasma cells were found in sternal marrow of 86 per cent of patients and varied from 6 7 to 83 6 per cent of total cells In only five cases were results of sternal marrow aspiration equivocal Eighty six per cent of patients were anemic red cell count averaging 3 090 000/cu mm Anemia was usually normochromic and normocytic Macrocytosis was rarely of sufficient degree and anemia sufficiently severe to suggest pernicious anemia

Eighty six per cent of patients had x ray changes the commonest being generalized osteoporosis which was

sometimes the only x ray abnormality Flea bitten or punched out areas were characteristic Bones involved in order of diminishing frequency were vertebra skull ribs pelvis clavicle femur humerus scapula fibula mandible and radius

Rouleaux formation present in 60 per cent increased sedimentation rate and made blood counting and typing difficult Excessive rouleaux formation occurs in other disorders associated with hyperproteinemia In addition Wright stained peripheral blood smears showed a peculiar bright blue coloration which was attributed to elevated plasma protein

Fifty seven per cent of patients had renal insufficiency Its pathogenesis is disputed Blood calcium concentrations over 11 mg per cent were found in 53 3 per cent Blood phosphorus values were elevated in renal failure Alkaline phosphatase activity was greater than 4 Bodansky units in 48 per cent and blood acid phosphatase units invariably normal Wassermann reaction was positive in 25 per cent Plasma cells were found in peripheral blood in 25 per cent

Average prognosis from onset was 21 months and longest survival 5 years Stilbamidine® or x ray therapy relieves pain but does not prolong life

Six abnormalities of special diagnostic significance are stressed hyperproteinemia or hyperglobulinemia rouleaux formation and the bright blue coloration of Wright stained blood unexplained anemia in older persons (warrants sternal aspiration) Bence Jones protein elevation of serum calcium and alkaline phosphatase and osteolytic bone processes and/or osteoporosis Electrophoretic study of patients with hyperproteinemia and/or hyperglobulinemia may reveal patterns strongly suggesting the diagnosis

Bone Marrow on Sternal Aspiration in Multiple Myeloma By study of the literature and sternal marrow aspirations in 51 cases of multiple myeloma Edwin D Bayrd[4] (Mayo Clinic) attempted to elucidate the type of

[4] ...987 1018 S pt mbe 1948

cell or cells involved in production of multiple myeloma to determine the origin of this cell or cells and to establish cytologic criteria for degree of malignancy

In general the pathologic cells seen in bone marrow smears in multiple myeloma resemble plasma cells and vary from the very anaplastic and immature cell to the well differentiated and almost characteristic plasma cell Cell size varies greatly even in the same case. In some instances uniformity of size and shape is the rule in some moderate variations occur and in still others very bizarre appearing cells (Fig 81) are observed varying greatly in size and shape but with almost indistinguishable gradations between stages

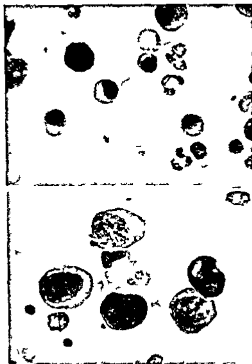
The feature which the myeloma cell shares with the plasma cell is the abundant granular basophil cytoplasm which tends to be fragile and undergo the same degenerative changes in each namely formation of Russell bodies and vacuolation Occasionally a perinuclear clear area or Hof is present and the nucleus tends to be eccentrically placed Cytoplasmic extensions or pseudopodia may be seen in either type cell but they occur more often and more dramatically in multiple myeloma than in other conditions Multinucleated cells are common

In addition myeloma plasma cells often have a large clear nucleolus and a leptochromatic nucleus and tend to form isolated areas of condensed chromatin Cytoplasmic extrusions or free cytoplasmic bodies occasionally with Russell bodies and vacuoles are almost universally present

All cases studied were of the plasma cell type In these cases the myeloma plasma cell constituted 25 90 per cent of the leukocytic elements Bayrd believes that all the so called types of multiple myeloma are merely variations in differentiation of this same cell

Anaplasia hypernucleation and lack of plasma cell predominance in certain cases were diagnostic pitfalls In more than a quarter of the cases myeloma plasma cells were not the predominant cell In most of these lymphocytes were present in equal o

From the histogenetic standpoint the least differentiated cells in a tumor are the ones that reveal its origin In the immature myeloma cell a granular finely reticular (leptochromatic) skeinlike chromatin was frequently en



F g 81—Ill t t m d f m m m f m sam p t t d m b t m dly d g ow n m lt pl f n pl my l m d d pl om ph m wh h m y ex t d f om × 725 (C t y f B y d L D Blood 3 987 1018 S ptemb 1948)

countered This adds support to the hypothesis that the myeloma cell is derived from reticulum

Cases in which there was a marked degree of pleomorphism often associated with frequent mitoses and notable immaturity had the poorest prognosis Of the

10 patients whose smears exhibited these characteristics none survived more than 12 months after onset of symptoms Of seven patients whose smears showed a majority of uniform mature appearing plasma cells three died at the end of 42 60 and 71 months respectively and four were living when last heard from after 24 26 88 and 67 months

Recent Studies of Multiple Myeloma Sternal and Rib Puncture and Results of Treatment with Stilbamidine[5] *are reported by Simon Propp L Whittington Gorham and Samuel Kantor (Albany Med College) Multiple* myeloma has been considered a neoplasm of the bone marrow in which cytology varies depending on the type of marrow cell involved Sternal marrow aspirations have now shown that multiple myeloma is in most instances a neoplasm of the plasma cell The disease is invariably fatal within a period of a few months to six years or longer after diagnosis is made Treatment with x ray nitrogen mustard and radioactive phosphorus has not been curative Stilbamidine* was first used because of its value in visceral leishmaniasis which like multiple myeloma is characterized by hyperglobulinemia In the original report on use of this drug together with a low protein diet in multiple myeloma 10 of 11 patients were relieved of pain In some patients osteolytic lesions did not expand for some time after treatment although no change in percentage of myeloma cells was detected

The authors administered stilbamidine* to six patients with multiple myeloma Injections were given intravenously 50 mg the first day 100 mg the second and 150 mg daily thereafter for a total of 20 treatments One patient received only two injections The drug was dissolved in 10 cc sterile distilled water and used immediately Atropine sulfate 1/150 gr was given hypodermically 30 minutes before each injection to minimize vasomotor reaction Sternal marrow aspirations were done in all patients before and after treatment and rib marrow punctures were performed on ccasions

(5) Blood 4 16 55 Ja ary 1949

Of the several diagnostic measures used only the mar row aspiration revealed evidence of the disease in all six patients Bone pain was present in only three osteo porosis was present in three Bence Jones protein was found in the urine of three Hyperglobulinemia was found in five patients and red blood cells clumped in Hayem s solution in three Anemia was present in five patients albuminuria in five azotemia in three and rapid red blood cell sedimentation in two of four patients tested

This study supports the theory that multiple myeloma is derived from a dysplastic line of plasma cells In con firmation of Snapper s original observation large baso philic inclusion bodies were demonstrated in cytoplasm of myeloma cells after treatment with stilbamidine*

Relief of pain occurred in two patients One was on a low animal protein diet and diet was unrestricted in the other Despite relief of pain and vertigo in one patient during treatment with stilbamidine* osteolytic lesions were observed to enlarge Trigeminal neuropathy re ported to occur several months after treatment developed in one patient No arrest or remission in course was ob tained in the five patients treated with stilbamidine*

Urethane (Ethyl Carbamate) Therapy in Multiple Myeloma was investigated by J Philip Loge and R Wayne Rundles[6] (Duke Univ) Ability of carbamic esters to suppress plant growth has been known for many years Mitosis is blocked in the pseudometaphase and irregular formation of monstrous nuclei results During the past few years ethyl carbamate has been given to patients with malignancy Experience has been that in disseminated cancer it is rarely beneficial In localized lymphomas roentgen irradiation remains the treatment of choice In acute leukemias there is usually no improve ment and in chronic leukemia benefit of carbamate ther apy is less than that of standard treatment Exceptional therapeutic results have been achieved however in mul tiple myeloma

Multiple myeloma is a malignant disease resulting from excessive proliferation of abnormal plasma cell within bone marrow Therapy in the past has been unsatisfactory The authors administered urethane to four patients with multiple myeloma General clinical improvement appeared during the second and third week of therapy when skeletal pain and fever began to subside Physical activity soon became tolerable within limitations imposed by skeletal disease The two patients with most extensive areas of skeletal destruction were able to perform ordinary activities and do light work without discomfort within four to six months of start of treatment

Progressive fall in hemoglobin and red cells ceased after one to two weeks of urethane but notable regeneration of blood did not begin before four to six weeks Blood values gradually improved toward normal several weeks after termination of urethane therapy Initial bone marrow aspiration showed abnormal proliferation of myeloma cells in all patients Repeated bone marrow aspirations in three patients after therapy revealed decrease in number of myeloma cells and appearance of monstrous cells similar to those observed in plants Variation of cell size densely staining cytoplasm and eccentric and pyknotic nuclei of the myeloma cells persisted after urethane administration

Initially all patients had hyperglobulinemia with reversal of albumin globulin ratio In three patients serum globulin fell and albumin rose to restore normal ratios during the period of aftertreatment follow up Dye excretion by kidneys was impaired in two patients before treatment During the weeks after treatment nitrogen retention did not develop and both albuminuria and Bence Jones proteinuria diminished X rays taken over a period of months after urethane therapy revealed no evidence of progression of skeletal lesions

During the first three or four weeks 4-6 Gm urethane was given daily by mouth in divided doses in the form of elixir or sirup Because of leukopenia d[illegible] reduced

to 2 Gm daily Urethane was given for about two months and then discontinued Total dose per patient varied from 120 to 240 Gm Treatment and post treatment observation period ranged from 7 to 13 months Two patients relapsed and were given a second course of treatment

[This use of urethane is decidedly worth further study—Eds]

In Vitro Studies of Lymph Nodes Involved in Hodgkin s Disease Tissue Culture Studies, Formation Behavior and Significance of Multinucleated Giant Cell Antonio Rottino[7] (St Vincent s Hosp New York City) found many multinucleated giant cells in cultures of lymph nodes affected by Hodgkin s disease Similar cells appeared in tissue cultures of many organs from many diseases but rarely were these cells present in is large numbers as in tissue cultures from nodes affected by Hodgkin s disease The significance of these cells remains doubtful

The consensus is that the cells bear no direct histogenic relationship to Sternberg Reed cells It seems more likely that they are foreign body giant cells Rottino found similar cells in tissue cultures of tuberculous and lymphosarcomatous nodes and nodes affected by nonspecific adenitis as well as in cultures of the buffy coats of centrifuged blood of normal human beings and cultures of normal spleens and nodes It is hypothecated that the as yet unidentified substance causing growth of these giant cells is a metabolite originating in tissues grown in vitro The claim that this substance is related to the specific cause of Hodgkin s disease and is a virus remains speculation

Interrelationship of Hodgkin s Disease and Other Lymphatic Tumors Cellular structure of lymphatic tumors is extremely labile and transition from one apparently distinct type to another is frequently observed Since all cellular components of lymphatic tissue are derived from the same mesenchymal stem cells this is not surprising Thus whereas differential diagnosis of

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scopic pattern even though the picture was often a mixed one

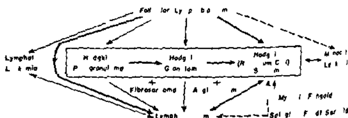
Transitions actually observed in this series are shown in Figure 82 A virtually complete alteration in histologic pattern of the tumor was noted in 39 per cent of 138 autopsied cases in which biopsies were available and in 31 per cent of 69 cases with serial biopsies Still more striking the incidence of pure type tumors in these two groups was only 19 and 23 per cent respectively When only one observation was made either of autopsy (62 cases) or biopsy material (431 cases) unmixed pictures were found in most cases This may have represented either an early phase before transition was initiated or a late one after the pattern was finally established In both the biopsy autopsy and serial biopsy series the most common change was from Hodgkin s granuloma to Hodgkin s (reticulum cell) sarcoma Next in order was Hodgkin s paragranuloma to granuloma Variety of histologic appearances observed in different foci in the same individual and even in several areas in the same lymph node was spectacular Thus 384 of 700 cases presented combined lesions

The 600 lymphomas not grouped with Hodgkin s disease exhibited alteration of histologic structure in much the same fashion (Fig 82) This series included many cases of reticulum cell sarcoma which obviously did not develop from Hodgkin s paragranuloma or granuloma being found either in pure form or as a result of a direct transition of follicular lymphoblastoma or lymphosarcoma Tumors at first classified as reticulum cell sarcoma also ended as lymphosarcoma Chronic lymphatic leukemia sometimes preceded development of large tumefactions indistinguishable from lymphosarcoma and patients with typical lymphosarcoma occasionally produced the blood picture of lymphatic leukemia

This study confirms and extends the opinions of others that a rigid subclassification of lymphatic tumors is artificial and confusing These 1 300 lymphatic tumors showed a striking fluidity in histologic pattern with

Hodgkin s disease and reticulum cell sarcoma or of lymphosarcoma and chronic lymphatic leukemia would seem to make a great deal of difference actually it makes little or none All are malignant mesenchymal tumors which vary only in degree and type of differentiation

For some years R Philip Custer and William G Bernhard[8] have been aware of the fluidity existing among tumors of lymphatic tissue and an assignment to examine and report on all lymphatic and hemopoietic tissues submitted to the Army Institute of Pathology during World War II offered a unique opportunity for detailed study Principal emphasis was on Hodgkin's disease Any case in which this diagnosis was not completely acceptable on the basis of either biopsy or autopsy specimens was discarded Final Hodgkin s material comprised 700 cases An additional series of 600 cases contained lymphomas apart from Hodgkin s disease (follicular lymphoblastoma lymphosarcoma reticulum cell sarcoma lymphatic leukemia monocytic leukemia) This group displayed transitions and combinations which furnish data to complete a scheme of interrelationship (Fig 82) For Hodgkin s disease the histologic classification of Jackson and Parker (paragranuloma granuloma sarcoma) was used on the basis of predominating micro



F g 8 —Tran t o act ally ob e d between the s ver l v ia t of m l gnant lymphoma (n t t b con t ed as ind cat ng ge et c eq) He vy l s sho t n t o m st ofte fou d l ght r l nes th se l s com mon Doubl head d a rows s gn fy a hang in th r d ect n Dotted l s d n t transt ns n t e count ed n this s es b t wh ch ha be n sec rep rted elsewh re

(8) Am J M Sc 216 625 64 De emb 1948

the neoplastic changes This is probably nature s way of performing the experiments described in the first two articles of this chapter — Eds]

Effect of Antireticular Cytotoxic Serum Observations on Cases of Hodgkin's Disease Joseph W Abernethy George T Harrell Leslie M Morris Henry L Valk and Kenneth M Cheek[1] (Winston Salem) undertook to confirm or disprove Russian reports that functions of the reticuloendothelial system are stimulated by serum prepared by injection into horses of cells derived from the spleen and bone marrow of uninfected human cadavers Rationale of its use is that material which is toxic to cells in large doses may stimulate them when given in mall amounts

Long investigation has lead Russian investigators to consider that connective tissue has definite physiologic functions (1) trophic—maintenance of cellular nutrition and of the hematoparenchymal barrier and cellular metabolism of proteins lipoids bile and iron (2) plastic—healing of wounds and fractures (3) protective—phagocytosis of bacteria formation of antibodies reaction to neoplasms (4) autoregulative—the internal secretion of stimulating substances found in the spleen (5) mechanical—maintenance of osseous and elastic tissue

Tests used by the authors to evaluate the effect of the so called antireticular cytotoxic serum on these connective tissue functions were designed originally by Russian workers Serum was administered to seven patients with Hodgkin s disease undergoing x ray treatment

Alterations in differential white blood cell count and sedimentation rate reported by Russian workers were confirmed but the degree and duration of change were not impressive Alterations in the Weltmann serum coagulation band were slight but tended to follow changes in sedimentation rate The authors were unable to find experimental evidence to support the Russians thesis that sedimentation rate is a measure of the porosity of

(1) North C 1 M J 9 341 350 J ly 1948

transitions and combinations that can best be interpreted as indicating a single neoplastic entity having a number of variants

Skeletal Lesions in Hodgkin's Disease Since 1938 Ernest H Falconer and Maurice E Leonard[9] (Univ of California) have studied aspirated sternal marrow from 59 patients with Hodgkin s disease in order to accumulate data in regard to bone marrow involvement in this disease Marrow specimens were obtained from 20 patients at autopsy from 12 of these sternal marrow had also been aspirated during life In 47 patients sternal marrow was aspirated during life after diagnosis had been confirmed by surgical biopsy of an enlarged lymph node

These studies showed that Hodgkin s disease spreads through the reticuloendothelial system as well as through lymphatic tissue A uniform cellular pattern was demonstrated in the aspirated marrows myelocytic elements were increased (shift to the left) with emphasis on neutrophilic and eosinophilic myelocytes band neutrophils eosinophilic segmented cells and plasmacytes The same cellular pattern was present in aspirated sternal marrow of 12 patients 10 of whom showed Hodgkin s lymphogranuloma in marrow at autopsy Marrows of 67 patients including 18 on whom autopsy was done showed an increase in megakaryocytes when enumerated by special technics with an established normal This increase of megakaryocytes is interpreted as a sign of marrow irritation and possible degenerative cellular changes

Incidence of skeletal lesions shown by x ray is misleadingly low because marrows with Hodgkin s lymphogranuloma may contain lesions too small to involve adjacent cortical portions of bone

[As Symmers reported in 1924 the bone marrow in Hodgkin s disease may show hyperplastic changes particularly in the eosinophils and eosinophilic myelocytes or it may be replaced by tissue of identical composition with that of the diseased lymph nodes Thus as pointed out by Furth in experimental leukemias in mice hyperplastic changes of a nonspecific type frequently accompany

(9) A Int Med 9 1115 1131 Dec mbe

Twenty patients receiving 24 courses of therapy were benefited Indirectly three other patients benefited through apparent resensitization to x rays Improvement was usually characterized by immediate disappearance of fever itching and pain Brownish pigmentation of the skin decreased in several patients as did Hodgkin s skin lesions splenomegaly hepatomegaly and adenopathy Remissions lasted an average of 2 8 months The longest were four five and six months

An immediate toxic reaction of nausea and vomiting occurred consistently after nitrogen mustard therapy Skin lesions macroscopically similar to those frequently seen in Hodgkin s disease appeared in a number of patients It cannot be stated whether this was a cutaneous spread of Hodgkin s disease after nitrogen mustard or a toxic effect resulting from local or systemic vascular damage The most serious complication of nitrogen mustard therapy resulted from bone marrow and lymphoid tissue destruction Leukopenia below 2 000 white cells/cc blood was recorded after 22 courses The fact that lymphocytes were the first cellular element to be decreased in peripheral blood suggests that the lymphocyte is the most rapidly destroyed of the formed elements of the blood That the destruction of blood cell elements results from a central as well as a peripheral toxic effect is demonstrated by the concomitant destructive hypoplasia and aplasia of the bone marrow when the peripheral count is lowest Appearance of hyperplasia of bone marrow and increased numbers of young form of myeloid and erythroid elements as well as megakaryocytes while the peripheral cellular elements are increasing during the recovery phase indicates the temporary nature of thi toxic effect Bone marrow involvement by the Hodgkin s disease process before therapy is therefore not considered a contraindication to nitrogen mustard therapy No apparent relationship was found between amount of measurable damage to the hemopoietic and lymphoid tissues and occurrence of clinical remissions

Since lymphocytopenia with a reversed monocyte

the hematoparenchymal barrier Studies of plasma and blood specific gravities hematocrit levels and total serum proteins offered no evidence that fluid or protein was lost from the vascular system after administration of serum

The Russians reported increase in rate of spread of trypan blue as evidence of increased activity of macrophages No such change could be demonstrated in the present studies Histamine wheal and saline absorption studies demonstrated no change in circulation of extravascular fluid No studies demonstrated the reported alteration of the hematoparenchymal barrier The experiments also failed to demonstrate the increase in phagocytosis of bacteria after administration of serum which was reported by the Russians

Results of use of antireticular cytotoxic serum as an adjunct to therapy in Hodgkin s disease were disappointing but no harm was thought to have resulted The authors may not have duplicated the conditions of the Russian experiments since the Russian workers used much smaller doses of serum and the titer of serum they used is not known

[Because of the mystery attached to many things of Russian origin the question of the value of so called antireticular cytotoxic serum in patients with neoplastic disease is sometimes raised by physicians and laymen For this reason this article is included.—Eds]

Studies in Hodgkin's Syndrome Nitrogen Mustard Therapy Robert P Zanes Jr Charles A Doan and Herman A Hoster (Ohio State Univ) treated 31 patients with Hodgkin s disease with a total of 44 courses of the nitrogen mustard methyl bis(β chloroethyl)amine hydrochloride The dose was 0 1 mg drug/kg body weight for five days for all but seven patients who received a double dose on two consecutive days and a single do e on the third day Each dose was dissolved in 10 cc saline and injected via a tube through which normal saline was being administered intravenously From 200 to 500 cc. saline was infused during each injection of nitrogen mustard

( ) J Lab & Cl n M d 33 100 1948 August

Remissions lasted less than 50 days in 41 7 per cent 35.2 per cent had good responses lasting 50-331 days

A single course of HN was given 23 patients 11 received two courses 9 three courses 4 four courses 2 five courses and 1 eight courses Results obtained with successive courses were roughly comparable to the composite results for all courses with the same proportion of successes and failures

Thirty one patients were regarded as having become resistant to x ray therapy and in 13 of these all of whom appeared to be running a progressively downhill course good remissions followed therapy Only four patients received HN as the first therapeutic procedure a number too small to permit statistical evaluation It appears however that the remissions are of much shorter duration than those usually following roentgen therapy Remissions appear to be definitely longer if combined HN and x ray therapy is administered

Constitutional symptoms such as fever night sweats weakness and itching usually responded exceedingly well to HN therapy Many previously incapacitated patients were completely rehabilitated for several weeks to months after a single course of therapy Adenopathy and splenomegaly regre sed in 70 2 and 71 7 per cent of cases respectively Lymphoid masses previously resistant to x ray therapy appeared to become more sensitive to x ray after HN therapy

Slight but definite fall in erythrocyte and hemoglobin levels occurred within five to six days after institution of therapy Granulocytopenia was maximal 21 25 days after therapy and leukocyte level then gradually returned to normal Progressive but temporary marrow hypopla ia followed nitrogen mustard therapy in 11 cases studied with serial marrow punctures the marrow picture usually returning to normal within six to eight weeks

The authors conclude that nitrogen mustard is a useful drug in treatment of Hodgkin s disease particularly in severe cases with marked constitutional symptoms In relatively early cases x ray therapy is the treatment of

lymphocyte ratio is frequently observed during the active phase of Hodgkin's disease regeneration of lymphocytes and return of the monocyte lymphocyte ratio toward normal was the most consistent laboratory finding associated with clinical remission

Nitrogen Mustard Therapy in Hodgkin's Disease Analysis of 50 Consecutive Cases is presented by William Dameshek Louis Weisfuse and Tobias Stein[3] Diagnosis of Hodgkin's disease was made in almost every instance by biopsy of a suitable enlarged peripheral lymph node Patients were 29 males and 21 females the majority under age 35 and most of whom had advanced disease with constitutional symptoms in addition to the local disease

Because of frequent occurrence of venous thromboses when nitrogen mustard (HN) was dissolved in 10 cc saline and injected directly into veins it became the practice early in this series to inject the material into rubber tubing of a freely flowing saline infusion A course of therapy consisted of four to six injections of nitrogen mustard administered on successive or alternate days An initial dose of 4 5 mg was given the first day If this amount was well tolerated succeeding doses were increased by 1 mg

Nausea and vomiting occurred in 93 2 per cent of patients it usually began one to three hours after injection and lasted two to four hours Shaking chills were observed in 12 4 per cent Fever either followed chills or occurred independently in 6 8 per cent

During the first three years of these studies only patients in a terminal state or with radioresistant disease were subjected to therapeutic trial Results in this group were not as good as those obtained in patients with less advanced disease treated during the past year However for purposes of analysis all patients are grouped together

Of the 50 patients treated with 102 courses of HN 79 4 per cent had a complete or partial response to therapy Duration of response ranged from 17 to 331 days

(3) Blood 4 328 379 Ap 1 1949

to remove chiefly red and white cells and plasma transferred to a silicone coated test tube Platelet counts of the two plasmas showed that generally fewer than 20 000 platelets/cu mm remained in the first but the second plasma consistently showed platelet counts higher than in whole blood High and low content centrifuged plasmas were mixed in varying proportions to a volume of 2 cc and beginning of coagulation clot retraction and prothrombin consumption determined

Results obtained clearly explain why the role of platelets has frequently been underestimated Coagulation began nearly as early in plasma with few platelets as in plasma with a large number Furthermore since coagulation begins at the top of plasma end point for coagulation time is reached exceptionally early because sufficient fibrin is formed to prevent flow of blood [on inversion of the tube—Ed] long before actual coagulation is complete Thus not only is coagulation time technically unreliable and misleading but it is also physiologically faulty because it measures behavior of blood under totally artificial surroundings and not a t functions in the lumen of a blood vessel after injury Far more accurate as a quantitative test of platelet function is consumption of prothrombin and speed and extent of clot retraction The greater the number of platelets the more rapid prothrombin consumption was Below a certain number of platelets no consumption of prothrombin could be demonstrated though coagulation still occurred since even with extreme care some platelets disintegrate and consequently some thrombin forms and even a minute amount of thrombin can convert a considerable quantity of fibrinogen to fibrin within confines of a test tube Clot retraction correlated well with prothrombin consumption and with number of platelets that is the greater the number of platelets the sooner clot retraction began and the smaller the final clot An important factor about clot retraction is that it is influenced markedly by bulk of cells Retraction is most complete in cell free platelet rich plasma In polycythemic blood retraction is poor even though platelets may be above normal simply because relatively weak retractive force cannot cone

choice primarily because remissions last longer than with HN_2. It is possible that the best form of therapy even in early cases may be a combination of HN and x ray the HN being given for its effect on proliferating cells which may either be at a distance from the local lesion or so situated as to remain untouched by x ray

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PURPURAS

The articles in this section are concerned with conditions resulting in spontaneous hemorrhage due either to defective platelets or to capillary fragility or perhaps to a combination of the two. With usual technics no obvious coagulation defect is noted in blood spontaneously or artificially rendered poor in platelets. The first article by Quick an outstanding authority in this difficult field demonstrates that prothrombin consumption and clot retraction in vitro indicate a definite defect of the coagulation process in a person with thrombopenia. The three articles following present other aspects of the problem of platelet function.

A very useful advance in the study of blood coagulation has been the introduction by Jaques of a method of coating laboratory apparatus with a nonwettable surface of silicone. With care on venipuncture to avoid the introduction of tissue thromboplastin the blood may be said to be maintained under almost intravascular conditions. At least coagulation of the blood in test tubes may be long delayed without the use of anticoagulants —Eds

Role of Platelets in Coagulation of Blood Either platelets play no direct role in coagulation or they are the key to the whole hemostatic mechanism. Armand J Quick Jacob N Shanberge and Mario Stefanini[4] (Marquette Univ) present observations that help to settle this basic problem. They studied platelet function quantitatively by varying the number of platelets without changing environmental conditions and correlated effect on coagulation time speed of clot retraction size of clot and consumption of prothrombin

TECHNIC —Blood obtained from young adults by venipuncture was placed in silicone-coated centrifuge tubes. Half the blood was centrifuged for 15 minutes at 4 000 rpm. Plasma so obtained was then transferred to another tube and centrifuged 10 minutes at high speed to remove platelets. The other half of the blood was centrifuged at 800 rpm for 10 minutes

(4) Am J M Sc 217 198 205 February 1949

pura and low platelet counts coagulation was normal but prothrombin consumption abnormally diminished These findings can be regarded as showing unequivocally for the first time a definite coagulation defect masked by normal coagulation time

Platelet Adhesiveness In an attempt to evaluate the clinical usefulness of the method for estimating platelet adhesiveness which was described by Helen Wright in 1941 Murray Weiner Kurt Zeltmacher Carl Reich and Shepard Shapiro[5] (New York Univ) studied curves of platelet adhesiveness in 110 instances under normal conditions and in a large variety of disease states

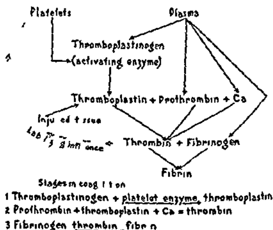
TECHNIC—Within 10 minutes after venipuncture 2 ml oxalated blood is pipetted into a glass tube with a bulbous dilatation at one end and the tube rotated at 7 rpm Samples for serial platelet counts are withdrawn before rotation is begun and every 20 minutes for 80 minutes Serial platelet counts are calculated in terms of percentage of initial count and a curve is plotted with number of remaining platelets as ordinate and time in rotating tube as abscissa The curve then represents the proportion of platelets which have failed to adhere to the wall of the rotating tube In normal persons platelet counts usually fall to about 30 per cent of the initial count in 80 minutes

No abnormality in platelet adhesiveness was demonstrated in a large variety of diseases in which disturbed coagulation was not a factor Platelets from hypercoagulable blood occurring spontaneously in association with thrombosis or artificially induced by large doses of vitamin K showed generally increased adhesiveness In spontaneously occurring hypercoagulability the change was not constant instances of normal adhesiveness occurring even in the presence of marked thrombocytosis Hypocoagulable blood whether incident to a blood dyscrasia or induced by dicumarol® was more consistently accompanied by decreased adhesiveness of platelets In hemophilia platelet adhesiveness increased beyond the premedication level when the coagulation defect was corrected by fraction I derived from human plasma In two patients with hemorrhagic phenomena deficient

(5) Blood 3 1275 1 8 N mb 1948

with the large cell mass and reduce its bulk Conversely anemic blood shows relatively good retraction

Present findings substantiate further Quick s hypothesis that platelets on disintegration liberate an enzyme which is essential for conversion of thromboplastinogen to active thromboplastin Reaction between thromboplastin and prothrombin has been shown to be stoichiometric therefore the amount of thromboplastin made



F g 83 —Co lat on of fact r part pat g n co gulati n act on (Courtesy of Q i k A. J t al Am J M Sc 217 198 205 Februa y 1949)

available is directly measured by prothrombin consumption test This hypothesis is presented in Figure 83

An explanation can now be given for the paradoxic observation that coagulation time is *generally normal* in thrombocytopenic purpura A minute amount of platelet enzyme can produce enough thrombin to coagulate sufficient fibrinogen in five minutes to form a clot rigid enough to give the coagulation time end point Clotting time therefore is apparently normal but this does not signify that coagulation is normal for determination of *prothrombin consumption* shows that *only a trace of* prothrombin is converted during the first hour after coagulation In two patients v

on clotting of normal plasma is inversely related to platelet concentration It is therefore concluded that the increased susceptibility of thrombocytopenic blood to heparin is a direct manifestation of decreased platelet concentration and does not necessarily indicate presence of a heparin like substance Amount of active heparin in normal plasma is very small (0 0005 mg per cent or less)

It is suggested that the number of platelets in blood may influence the heparin tolerance test

Clotting Behavior of Human "Platelet Free" Plasma Evidence for Existence of 'Plasma Thromboplastin." The precise role of platelets in blood coagulation has long been a matter of debate Studies on the function of platelets in coagulation have been hampered by the difficulty of rendering plasma to which no anticoagulant has been added platelet free before spontaneous coagulation occurs C Lockard Conley Robert C Hartmann and William I Morse II[7] (Johns Hopkins Univ) prepared human platelet free plasma by use of silicone treated apparatus and high speed centrifugation and determined its clotting behavior

TECHNIC—Needles syringes test tubes and pipets were treated with silicone after the method described by Jaques In withdrawing blood in order to avoid contamination with tissue juice a multiple syringe technic was used the contents of the fr t syringe being discarded From 30 to 40 ml blood from th second syringe was carefully placed in iced silicone treated tubes and centrifuged at 7 000 rpm at 4 C for five minutes to remove cells and most of the platelets The upper portion of the plasma was removed with a silicone treated pipet and r centrifuged at 12 000 14 000 rpm for 10 minutes Ther aft r the upper portion of this plasma wa removed and stor d in silic ne treated tubes in an ice bath Normal plasma obtained in thi manner remains fluid at least several days at 4 C It was not always possible to obtain plasma entirely free ct ref actile bodies (considered to be platelets) However in me instances platelets appeared to be completely absent

Of the 86 subjects studied 41 were normal persons and the others had various diseases The most significant find

(7) J Cl I t gat n 28 340 35 31

platelet adhesiveness was the only demonstrable defe t in the coagulation mechanism

Platelet adhesiveness appears to depend on the in trinsic properties of the platelet surface (it is believed that fibrinogen is converted to fibrin on the platelet sur face and that adhesiveness results from this change) and on the character of the medium in which platelets are suspended Inhibition of the clotting mechanism should therefore impair the adhesive capacity of platelets and results of these studies confirm this hypothesis How ever the converse that augmented coagulability should accelerate adhesiveness was less constantly supported by the results Thrombosis appears to result from a com bination of events of which blood hypercoagulability may or may not be one Nevertheless it seems logical to as sume that in a given case detection of increased adhesive ness of thrombocytes warrants pursuit of the possibility that thrombosis is present or imminent

[This should be a useful type of observation to pursue in patients with normal numbers but seemingly defective function of platelets —Eds]

Relationship of Heparin Activity to Platelet Concen tration was studied by C Lockard Conley, Robert C Hartmann and John S Lalley[6] (Johns Hopkins Univ) The fact that more protamine sulfate is necessary to re store normal clotting time in thrombopenic blood than in normal blood has been interpreted as suggesting the presence of a heparin like substance in the blood in thrombocytopenic purpura Because of the possibility that the increased susceptibility of thrombocytopenic blood to heparin was the result of a thrombocytopenia it self the following experiments were conducted

TECHNIC —Platelet free plasma was obtained from normal persons without use of anticoagulants by high speed centrifuga tion at low temperatures Platelet rich plasma was obtained by low speed centrifugation After det rmination of platelet counts these two plasmas were mixed in different proportions and varying amounts of heparin were added Clotting times of these plasmas were then done

Results indicated that the inhibitory action of heparin

(6) P c Soc F per B ol & M d 69 284 287 N

normal whole blood clotting time This indicates that plasma thromboplastin is necessary for normal hemostasis regardless of clotting time in vitro Presumably anti hemophilic globulin is identical with the plasma thromboplastic precursor

Hemophilic blood presumably lacking in plasma thromboplastic factor clots if platelets are present although clotting is delayed and incomplete Likewise normal plasma clots in the absence of platelets but in this instance also coagulation is incomplete It appears that both the platelet and plasma factors are necessary for normal coagulation although either one alone suffices to initiate coagulation Nature of the interaction between platelets and the plasma factor remains to be elucidated

Platelet free plasmas of three patients with Hodgkin s disease treated with nitrogen mustard and of most patients with thrombocytopenia behaved normally

Study of Bone Marrow from 36 Patients with Idiopathic ***Hemorrhagic (Thrombopenic) Purpura and 50*** control patients was made by L W Diggs and J S Hewlett[8] (Cleveland Clinic) The principal value of bone marrow examination in cases of suspected idiopathic thrombopenic purpura is to exclude leukemia and aplastic anemia Bone marrow in idiopathic hemorrhagic purpura is hyperplastic There is a slight myeloid and erythroid immaturity and in some cases a slight eosinophilia and lymphocytosis

The average megakaryocyte count in the patients with purpura was 17/10 000 nucleated cells (range 3 59) and in normal persons was 16 (range 1 54) These results agree with observations of others that the number of megakaryocytes in idiopathic thrombopenic purpura is within the normal range

Although it has been believed that patients with high megakaryocyte counts have a good prognosis and will respond to splenectomy whereas those with low counts have a poor prognosis the authors found no correlation

(8) d 3 1090 1104 O t b 1948

ing was that normal platelet free plasma clots in a relatively short time in glass tubes at 37 C but its clotting time in silicone treated tubes is greatly prolonged and sometimes clotting does not occur This observation suggests that contact with glass activates some plasma constituent which can initiate clotting This factor is apparently activated slowly or not at all by contact with silicone treated surfaces The authors believe that with constantly perfect technic normal platelet free plasma would regularly be incoagulable in silicone treated tubes

No information is available concerning the origin and nature of this plasma factor It is possible that during manipulations involved in the experiments a few platelets were broken up However if active thromboplastic substance were liberated in this manner clotting time of platelet free' plasma should be the same in silicone treated and in glass tubes There is no evidence that a silicone surface itself interferes with clotting for on addition of highly dilute thromboplastin to platelet free plasma clotting occurs as promptly in silicone treated as in glass tubes The inescapable conclusion is that an inactive thromboplastin precursor in plasma is activated on contact with glass surfaces [Compare this with first article in section by Quick *et al* —Eds]

The authors studies show that platelets do not appear to be necessary to initiate clotting but they increase rate of clotting and amount of prothrombin consumed in the process There is close correlation between number of platelets present and amount of prothrombin converted during clotting in glass tubes

Hemophilic platelet free plasmas were invariably spontaneously incoagulable in glass and in silicone treated tubes at 37 C although they clotted promptly on addition of thromboplastin This suggests that the defect in hemophilia is a deficiency of the plasma thromboplastic factor It is apparent that hemophilia is not caused by any defect in platelets but rather that the presence of platelets is what makes hemophilic blood clot at all In one hemophiliac hemorrhagic diathesis pers -despite

Until discovery of platelets in 1842 purpura was considered simply a vascular disease Soon after this discovery purpura was classified as thrombocytopenic or nonthrombocytopenic Before this discovery it was impossible to differentiate purpura from hemophilia hypoprothrombinemia or fibrinopenia

With increasing study of disorders of the blood clotting mechanism interest in vascular phases of purpura dwindled Investigation of the origin and destruction of platelets however revealed that platelet destruction often accompanied experimentally produced anaphylaxis After the origin of platelets in the megakaryocytes was established it was found that platelet production was often diminished not only in bone marrow diseases such as leukemia and aplastic anemia but also in severe infection after massive x radiation and exposure to benzene and as a result of hypersensitivity Though it is well established that splenectomy results in increase of circulating platelets in patients with idiopathic thrombocytopenic purpura it is not known whether the spleen destroys platelets inhibits their development in bone marrow or controls their release from the marrow

Platelet reduction from hypersensitivity has been conclusively demonstrated in rabbits sensitized to horse serum but clinical proof has been somewhat less striking In some patients with granulocytopenia reduction of granulocytes after ingestion of offending allergens has been demonstrated as has platelet reduction after ingestion of allergenic food Removal of allergens from the diet has resulted in normal platelet counts Allergenic drugs producing thrombocytopenia have also been found

It is evident that allergy is one of several factors capable of producing thrombocytopenia and likewise is one of several factors capable of producing vascular changes characteristic of purpura In support of the hypothesis that an allergic subject might have both hematologic and vascular responses simultaneously to the same allergen is the clinical response of both thrombocytopenia and purpura to allergy control without splenectomy

between the number of megakaryocytes in marrow during the acute phase of the disease and prognosis with or without splenectomy Furthermore there was no apparent correlation between the number of megakaryocytes before and the platelet count after splenectomy in the 22 patients operated on

In idiopathic thrombopenic purpura the predominant cell in the megakaryocyte series was an intermediate megakaryocyte without platelet production in contrast mature platelet producing megakaryocytes predominated in normal marrows The differential counts were made by examining 25 or more megakaryocytes the principal criteria for differentiating the cells of the series being presence or absence of granules and of granular platelets Megakaryoblasts have no granules immature cells have a few fine granules unevenly distributed intermediate cells have coarse granules fairly evenly distributed but no well defined platelets and mature cells have coarse granules and form platelets

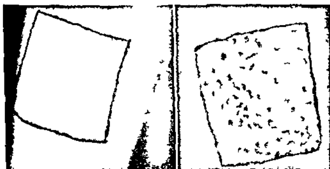
Marrow studies on two patients before and after splenectomy showed decrease in relative number of megakaryocytes and increase in number of platelet producing cells postoperatively There was no correlation between eosinophil counts and deaths recurrences or cures with or without splenectomy

The following two articles are concerned with an allergic basis for thrombocytopenic purpura Of especial interest are the observations on sedormid® a well known cause of thrombopenia in susceptible individuals —Eds

Role of Allergy in Pathogenesis of Purpura and Thrombocytopenia is summarized by Frederick W Madison[9] (Marquette Univ) Though previous attempts had been made to classify causes of purpura allergy was first suggested as a cause in 1808 In 1914 Osler established the importance of allergy as the etiologic factor in many patients with simple purpura without coagulation defect and several years later allergy was suggested as the cause of Henoch s and Schoenlein s purpuras

(9) Blood 3 1083 1089 October 1948

It was not possible to transfer the hypersensitivity of any of these patients to other subjects The action of two related open chain ureides adalin® and bromural® on clot retraction was investigated in two of the patients Adalin® reduced clot retraction in both and bromural® in one Reduction was significant but less than that produced by sedormid® Adalin® and bromural® failed to reduce clot retraction in eight control subjects Results of these tests suggest the danger of giving any open



F g 84 (l f) —C t l g b t g p pyl gly l n p t t wh h d d f m l m d® pu p
F g 85 (ght) —P t h t g f p f d m ® y t l t t d l t p pyl gly l m p t t
(C y f A k yd J F Cl S ? 49 85 1949)

chain ureide preparation to a patient who has recovered from sedormid® purpura

Agglutination of platelets and reduction in clot retraction by sedormid® and the positive results of patch testing with this drug provide a series of tests which may be helpful in diagnosis of sedormid® purpura Hitherto the only way in which diagnosis could be established was by administration of a test dose of the drug Danger of this method is obvious The author refuted a suggested diagnosis of sedormid® purpura in one patient by these laboratory tests and subsequently administered sedormid® without development of untoward symptoms

Pathogenesis of Thrombocytopenic Purpura Due to Hypersensitivity to Sedormid® (Allyl isopropyl acetyl carbamide) Among the many foods and drugs known to cause thrombocytopenic purpura sedormid® an open chain ureide hypnotic has frequently been described in European medical literature Studies of the pathogenesis of sedormid® purpura in three patients are reported b J F Ackroyd[1] (St Mary s Hosp Med School) In two of these patients administration of sedormid® after recovery from purpura reproduced the disease and in one of the two purpura was induced by a dose of sedormid® as small as 1 4 × 10^6 Gm

When sedormid® was added *in vitro* to blood taken from two of the three patients after recovery from purpura it caused platelet agglutination In the third patient no agglutination occurred No agglutination could be produced by adding sedormid® to the blood of eight control subjects No platelet lysis was observed in any of these preparations

Blood clot retraction was reduced by addition of sedormid® in all three patients This effect was produced by concentrations of sedormid® which might be expected to occur *in vivo* from therapeutic doses of the drug No similar effect was produced in the blood of 18 control subjects Reduction of clot retraction was attributed to the action of sedormid® on platelets

Application of sedormid® to the skin of two of the three patients after they had recovered from the attacks of purpura caused local hemorrhages without any fall of platelet count or general rise in capillary fragility Result of patch testing with sedormid® *in* one of these patients is shown in Figures 84 and 85 Figure 84 illustrates the area of skin used as a control and exposed only to propylene glycol Figure 85 shows the area of skin exposed to a suspension of sedormid® crystals in a saturated solution of propylene glycol No hemorrhages were produced in the third patient or in any of the 20 control subjects by this patch test

(1) C n Sc 7 49 85 1949

showed mas ive bilateral hilar adenopathy with clear paren chyma Aspiration of sternal marrow revealed 39 per cent poly morphonuclear leukocytes 19 per cent lymphocytes 14 per cent metamyelocytes II 13 per cent monocytes 14 per cent myelocytes 1 per cent reticulum cell 3 per cent megakaryo blasts and 1 per cent megakaryocytes 13 per cent normoblasts and 18 per cent erythroblasts

Oozing of blood from nose and gums continued and urine became grossly bloody Temperature fluctuated between 101 and 103 F The seventh hospital day the patient appeared con fused and the eighth day incomplete left hemiplegia developed and later in the day she died

Autopsy revealed sarcoidosis of the mediastinal lymph nodes lungs spleen and myocardium hemorrhage into the thalamu the left putamen and both lateral ventricles generalized pur pura of the skin and hemorrhage into the pericardium epi cardium endocardium pelvis of both kidneys mucosa of the urinary bladder stomach small intestine and retroperitoneum

CASE 2—Woman 23 was hospitalized because of recently developed ecchymoses of the right eye Though she had had menorrhagia for six years and recurrent spontaneous ecchy moses without trauma careful examination seven weeks before hospitalization had failed to reveal any other clinical abnormal ity Bleeding and clotting times had been normal and platelet count 100 000/cu mm Subsequently mild hypochromic anemia with a normal differential blood count and platelet count of 110 000 was found

At the time of hospital admis ion the spleen was just pal pable Bleeding time was 7½ minute prothrombin time 18 seconds clot retraction normal and capillary fragility tests normal Platelet count was 170 000 Sternal marrow revealed slight hyperplasia of megakaryocytes with numerous young forms

Histologic examination of the spleen after splenectomy re vealed sarcoid disease Platelet count rose to 260 000 two days after operation and despite the fact that later it fell to 140 000 she had no subsequent hemorrhagic epi odes *Serum albumin* concentration was 4 per cent and serum globulin 2 5 per cent Mantoux te t was negative in dilution of 1 10 000 and 1 100

[The single platelet count recorded for Case 1 ndicates no abnormality that fo Case 2 shows some reduction Whether these pat e t bl d because of thrombocytopen a is thus not clear —Eds]

Diffuse Platelet Thromboses with Thrombocytopenia and Hemolytic Anemia (Thrombotic Thrombocytopenic Purpura) Fifteen cases of a rapidly fatal acute anemia in which autopsy revealed multiple visceral hyaline

It is concluded that in sedormid® purpura there are two separate conditions a capillary defect and a deficiency in number of circulating platelets and that the latter tends to increase the hemorrhagic tendency due to the capillary lesion

Purpura Hemorrhagica Associated with Sarcoidosis Charles A Ribaudo Thomas J Gilligan and Antonio Rottino (St Vincent s Hosp New York City) add two cases to the six they were able to find in the literature It is of interest that in the reported cases total protein and globulin fractions were normal though serum globulin level is often elevated in sarcoidosis

CASE 1—Girl 18 was hospitalized because of an illness of 11 weeks duration in which for the first 3 weeks she had had fever to 100 6 F periauricular swelling and brown raised areas on the skin in the ankle region Despite the fact that these symptoms subsided a widespread rash developed which one week before admission turned purple Two days before admission bleeding from the nose and mouth began and ecchymoses were detected on the lower lip

She had had mumps at age 4 The only drugs taken during the past year were feosol® an ampule each of pitocin® and ergotrate® penicillin and sodium bicarbonate

Skin of the legs and thighs was covered with a diffuse multiform slightly raised purple eruption with lesions approximately 1 × 0 5 cm which did not blanch on pressure In addition there were oval areas about 0 5 cm in diameter on the dorsum of the forearms and occasional pinpoint purple spots in the same area Numerous pinhead sized purple black areas were present on the buttocks and there were hemorrhages into the right bulbar conjunctiva Numerous pinpoint petechiae were noted on the buccal mucosa

Red cell count was 3,710 000 hemoglobin level 11 6 Gm and differential blood count normal except for 3 per cent metamyelocytes Platelet count was 570 000 Prothrombin time was 17 second undiluted and 40 seconds diluted Serum bilirubin concentration was 1 4 mg but later rose to 3 1 mg Serum globulin was 2 1 mg and serum albumin 3 75 mg per cent Bleeding and clotting times were normal Blood cultures and Kahn test reaction were normal Mantoux test was negative in dilution of 1 100 000 During hospitalization bleeding time increased to 40 minutes but clotting time remained normal No evidence of blood sickling was detected Chest x rays

(2) A ch Int. Med 83 3 330 March 1949

curred and she became restless and dyspneic with weak thready pulse and periodic breathing Abdominal pain developed and blood appeared in the stools Hematologic findings were those of a typical hemolytic crisis Thrombocytopenia demonstrated the second day after bleeding from the bowel began persisted Throughout the remainder of the patient's course nausea and vomiting continued as did bleeding from bowel and vagina Temperature varied between 100 and 103 F and a bizarre and vacillating neurologic picture hematuria and striking mental deterioration developed She died four hours after splenectomy performed the ninth day

Autopsy revealed multiple hyaline thrombi in smaller blood vessels of the myocardium pericardium lungs liver spleen and lymph nodes Almost every thrombus was partly or completely surrounded by proliferated endothelial cells At times the thrombus appeared to have been largely replaced by small concentric masses of endothelial cells Figure 86 illustrates one of these thrombi in the lung Kidneys showed prominent glomerulitis involving every glomerulus seen Most glomeruli were without hyaline thrombi It seems therefore that the glomerular endothelial proliferation was for the most part not directly related to the hyaline thromboses These findings appear to be at variance with the common belief that the endothelial proliferation is strictly secondary to the thrombosis Mucosal infarction of the large bowel was also present

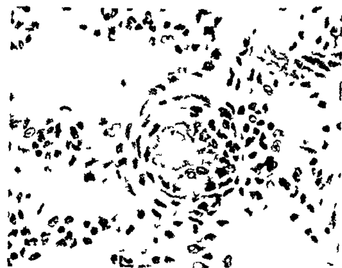
[This condition is to be considered whenever a rapidly developing type of thrombocytopenic purpura with severe neurologic and constitutional signs is encountered Septicemia especially meningococcemia must be excluded as another cause of purpura fulminans —Eds]

Thrombopenic Purpura Failure of Direct Blood Transfusion to Raise Platelet Level Review of the literature by John S Lawrence William N Valentine and William S Adams[4] (Univ of Rochester) revealed only two articles on effect of blood transfusions on platelet count in thrombopenic purpura In one two cases were reported and in the other three The authors report their experiences in attempts to elevate platelet count in two patients with thrombopenic purpura

CASE 1 —Man 37 had generalized petechial rash and bleeding from gums mucous membrane of the mouth and nose Aplastic anemia was diagnosed with aid of sternal marrow biopsy Platelet count was 4 000 6 000/cu mm Three hours after a direct transfusion of 690 cc blood platelet count was

(4) J Lab & Cl M d 33 10 7 1081 S pt mb 1948

thrombi within arterioles and capillaries have been reported in the literature Thrombi were frequently surrounded by proliferating cells from the vessel wall It is generally agreed that hyaline thrombi are composed of agglutinated blood platelets In presenting another such case I I Muirhead G Crass and J M Hill[3] (Baylor Hosp Dallas) mention an associated feature pre



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viously unemphasized namely a diffuse proliferative glomerulitis which for the most part was not associated with platelet thromboses

Girl 14 was hospitalized because of three episodes of transient paralysis of the left arm in the previous two weeks jerking of the left arm two days before admission jaundice and muscular weakness She did *not* appear acutely ill Physical examination revealed slight jaundice anemic appearance and multiple ecchymoses over the lower extremities The day after admission attacks of vomiting and multiple loose stools oc

(3) Am J Cl n Path 18 5 353 J ly 1948

Though favorable results from splenectomy have been reported by many observers equally satisfactory results have been reported from medical management Recurrence following splenectomy has also been reported previously

The relation of platelet count and bleeding tendency is important although there is some evidence that this is not the sole criterion of bleeding Critical platelet level has been estimated to be from 70 000 to 100 000/cu mm On one patient platelet counts were done every 2 weeks for 10 months During this period platelet count ranged from 11 000 to 70 000 but petechiae occurred on only three occasions During these bleeding phases no particular change in platelet count occurred

Hemorrhagic phenomena may be the result of abnormal function of the blood clotting mechanism or of a defect of the capillary wall or both Blood clotting requires collection of platelets at the site of injury followed by deposition of fibrin In thrombopenia clot retraction is defective possibly because excess platelets are required for this function The title thrombopenic purpura suggests that the platelet count has received chief emphasis in study of hemorrhagic manifestations of this disease Capillary wall defects have not gone entirely without consideration however Increa ed capillary fragility has been demonstrated by use of the tourniquet test The cause of capillary fragility is unknown Injection of histamine has b en shown experimentally to cause thrombopenia and increase in capillary fragility but there is no evidence that blood histamine is increased in idiopathic thrombopenic purpura

Two explanations have been offered to explain thrombopenia the suppression of megakaryocyte activity by the spleen and increased platelet destruction by the spleen If the spleen alone were involved splenectomy should produce consistently good results Since thrombopenia may recur after splenectomy even when careful earch has been made for accessory splenic tissue the author postulate that the whole reticuloendothelial sys

zero Next day count was 2 000 In two hours 1 500 cc whole blood was given by multiple syringe method Platelet count two hours later was 6 000 Bleeding continued

CASE 2—Man 53 had had splenectomy for idiopathic thrombopenic purpura and was hospitalized for a laparotomy to search for accessory spleens By means of a Pennell apparatus which consists of a short rubber tube between donor and recipient through which blood is milked by a rotating worm 1 500 cc blood was given in three hours Before transfusion platelet counts were 10 000 16 000 and after transfusion they were 50 000 80 000 Count fell to 24 000 28 000 two hours later and after another hour was 20 000

The authors produced substantial elevations of platelet counts which persisted several days in animals by cross circulation technics involving carotid to carotid anastomosis Under these conditions period of mixing was longer and larger amounts of blood were mixed than in the patients studied The authors suggest therefore that under different circumstances transfusion might elevate platelet count in thrombopenic purpura

[This report deals with a frequent clinical question as to the mode of action of transfusion therapy in the control of bleeding in thrombocytopenic purpura Presumably if the immediate demand for platelets were sufficiently great the transfused platelets could disappear from the blood stream without being adequate in number to control bleeding As suggested by the authors on the basis of animal experiments under less severe need for platelets transfusion might be effective in raising the platelet count —Eds]

Role of Splenectomy in Thrombopenic Purpura George Bogardus J Garrott Allen Leon O Jacobson and Charles L Spurr[5] reviewed records of 20 patients with idiopathic thrombopenic purpura seen at the University of Chicago Clinics during the past 20 years Among these patients uncontrolled bleeding was the chief indication for splenectomy Follow up periods from six months to two years revealed recurrences in 3 of 10 patients treated medically and in 6 of 10 whose spleens were removed Severe recurrences occurred in two of the surgically treated but in none of the medically treated patients It is not claimed that these statistics are sufficient for sound evaluation of splenectomy in treatment of this disease

(5) A h S g 58 16 27 J u y 1949

[The natural history of bleeding and recovery with or without splenectomy in thrombocytopenic purpura is so subject to individual variation that in our opinion no conclusions can be drawn from the above case history. Other authors have noted that no improvement followed removal of accessory spleens.—Ed.]

Experience with Antiheparin Compounds in Essential Thrombocytopenic Purpura. Both protamines and toluidine blue are capable of combining with heparin in such a manner as to inactivate the anticoagulant properties of heparin. Since it has been suggested that an increased amount of heparin-like substance is present in blood of patients with primary or secondary thrombocytopenia, Thomas W. Parkin, Byron E. Hall and Charles H. Watkins[7] performed protamine-heparin titrations on blood of patients with essential thrombocytopenic purpura and administered protamine and toluidine blue intravenously to a patient with essential thrombocytopenic purpura. The case follows:

Woman, 25, who had had a splenectomy 2½ years previously because of purpura, hypermenorrhea and thrombocytopenia, was hospitalized again with similar complaints. She was given 120 mg. protamine sulfate intravenously in four days and 312 mg. toluidine blue in 11 days. Despite this she continued to bleed from skin and mucous membranes, and platelet count and clot retraction and bleeding times were unchanged.

Blood from five normal control subjects and from three patients with essential thrombocytopenic purpura was titrated with amounts of protamine increasing from 0.012 to 0.039 mg. according to the method proposed by Allen and co-workers. Coagulation times of the blood of the three patients with purpura were essentially the same as those of the controls. No conclusions concerning presence of an excess amount of heparin-like substance in these patients could be drawn.

The authors suggest that the discrepancy between their results and those obtained by other workers may be accounted for on the basis of errors in the present protamine-heparin titration tests because such tests involve use of a compound (protamine) which has many different effects on different phases of the blood clotting

7. ( ) P St ff M t M Cl 3 309 316 J ly 7 1948

tem is involved in idiopathic thrombopenic purpura Splenectomy may be presumed to remove enough reticuloendothelial tissue to relieve many but not all patients

Recurrent Primary Thrombocytopenic Purpura with Accessory Spleens According to Philip Thorek Ralph Gradman and John S Welch[6] (Chicago) the incidence of recurrent primary thrombocytopenic purpura closely parallels that of accessory splenic tissue Embryologically splenic anlagen appear on the left side of the dorsal mesogastrium as several small hillocks the subsequent fusion of which forms a single organ Failure of fusion of these splenic masses results in the formation of accessory spleens Whether this abnormality occurs cephalad caudad or ventral to the main mass and whether it arises early or late in embryonic life determine roughly the location of the splenicule True accessory spleens are commonly found in the splenic hilus gastrosplenic omentum great omentum edge of the omentum splenocolic ligament pleurocolic ligament *peritoneum* along the splenic vessels and pancreas Splenic seeding may result from trauma to the spleen and should be considered during removal of the spleen for hemorrhagic diseases The importance of searching for accessory splenic tissue during operation is illustrated by the following case

Woman 22 was hospitalized because of pain in the right side for four days accompanied by vomiting and constipation She had been told that she had purpura 3½ years previously and 6 months later splenectomy was performed after profuse vaginal bleeding Since splenectomy she had had intermittent minor manifestations of persistent bleeding tendency and two severe episodes of vaginal bleeding

Platelet counts of 77,280 and 6 850 indicated the possibility of accessory splenic tissue and operation revealed three accessory spleens two in the omentum near the previously ligated splenic pedicle and one along the upper border of the tail of the pancreas After operation there was no dramatic cessation of bleeding but it gradually subsided and bleeding time and platelet count became normal One month later bleeding recurred and again platelet counts were low On reexploration no additional splenic tissue could be found She improved gradually and is still being followed

(6) A S g 1 8 304 311 Aug t 1948

had increased protamine titrations before therapy They received 41 treatments of which 27 halted the bleeding 7 lessened it and 7 were without effect Of two patients with excessive vaginal bleeding at puberty one had an increased protamine titration before and a decreased titration after therapy bleeding was stopped in both

Bleeding was not stopped by therapy in any of seven patients with idiopathic thrombopenic purpura nor were platelet counts increased Only three had increased protamine titrations before and decreased titrations after therapy Three of four patients with secondary thrombopenia had increased protamine titrations before and decreased titrations after therapy and in them bleeding was halted Bleeding was unaffected in two patients with prothrombin deficiency and in two with hemophilia

For vaginal bleeding protamine sulfate was more effective than toluidine blue The dose of protamine sulfate was usually 50 mg in 5 cc aqueous solution intramuscularly every four to six hours or 150 mg in saline solution given intravenously in one hour plus 50 mg given intravenously Bleeding associated with serious marrow disorders responded better to toluidine blue The authors current practice is to administer 6-8 mg toluidine blue kg body weight daily for three or more days The dye is dissolved in isotonic sodium chloride solution and passed through a Seitz filter for sterilization and removal of all undissolved particles It is administered intravenously over a two hour period Transient nausea and vomiting have been observed in about 15 per cent of patients given toluidine blue and occasionally after intramuscular administration of protamine sulfate pain occurs at the injection site but this reaction is minimized by careful injection technic

Although the protamine titration was increased in all the patients treated not all responded In some the increased titration was due to hemophilia in others to pronounced prothrombin deficiency Neither of these groups responded and the defect presented by thrombopenia did not respond or responded inadequately Thrombo

mechanism (In addition to neutralizing heparin protamine has been reported to have an antithromboplastic and an antiprothrombic action and to precipitate fibrinogen)

[The reader should also consult the abstract of the article by Conley Hartmann and Lalley (p 440) —Eds]

Abnormal Bleeding Response to Treatment with Toluidine Blue and Protamine Sulfate According to J Garrott Allen Burton J Grossman Richard M Elghammer Peter V Moulder Charles L McKeen Leon O Jacobson Mila Pierce Taylor R Smith and James M Crosbie[9] (Univ of Chicago) abnormal bleeding may result from a heparinoid disturbance in the clotting mechanism This heparinoid state resembles but is not identical with that produced by intravenous injection of commercial beef heparin The patients studied all of whom had spontaneous bleeding had a similar clotting abnormality characterized by increase in the protamine titration and frequently associated with prolongation in whole blood clotting time many also had moderate or severe thrombopenia The protamine titration was increased when prothrombin level was normal or near normal when fibrinogen levels were not abnormal and when fibrinolysin was not grossly disturbed In only rare patients was clotting time of whole blood sufficiently prolonged to delay appreciably the clotting of normal blood Most patients responded to adequate therapy with toluidine blue and/or protamine sulfate

Five patients with postpartum hemorrhage six with acute and two with chronic leukemia and bleeding three with radiation hemorrhage five with bleeding after nitrogen mustard therapy for Hodgkin s disease and two with bleeding secondary to uremia and nephritis all had increased protamine titrations before and decreased titrations after therapy with protamine sulfate and/or toluidine blue Bleeding lessened in all these patients and stopped in all but one with acute leukemia and one with Hodgkin s disease Of 32 patients with menorrhagia all

(9) J A M A 139 1251 1 54 Ap 30 1949

agulation In 1946 and 1947 conclusive evidence of the existence of this factor was obtained independently in three different laboratories and a case of deficiency of this factor was reported Addition of small amounts of the factor to purified prothrombin products increased prothrombin rate to that of native plasma Because this factor accelerates interaction of prothrombin thrombo plastin and calcium ions and because it is a globulin it has been given the name Ac globulin A similar but more potent accelerator in serum has been called serum Ac globulin to distinguish it from plasma Ac globulin

Experiments by Arnold G Ware and Walter H Seegers[9] (Wayne Univ) suggest that plasma Ac globulin is a completely inactive proenzyme which is partially activated (changed to the active catalyst serum Ac globulin) by amounts of thrombin too small to cause clotting of plasma Slightly larger quantities of throm bin completely activate the enzyme whereas greater amounts destroy its activity

In absence of Ac globulin thrombin formation is slow 1 1½ hours being required to produce a 30-40 per cent yield of thrombin from a mixture of prothrombin throm boplastin and calcium ion When plasma Ac globulin is added the yield of thrombin is 100 per cent during the first 11 minutes about 5 per cent of prothrombin is con verted to thrombin and during the next 2 or 3 minutes the remaining 95 per cent is converted When plasma previously activated with thrombin (presumably con taining serum Ac globulin) is added the period of slow thrombin production is reduced to about two minutes

Inert plasma Ac globulin is thought to be changed to serum Ac globulin by thrombin Fibrinolysin does not produce the change Serum Ac globulin is the active catalyst used in the interaction of prothrombin throm boplastin and calcium ion It is present in bovine serum and has been formed in oxalated plasma or from purified plasma Ac globulin by addition of small amounts of thrombin When the first small amounts of thrombin

[9] [illegible] 567 574 [illegible] 1949

penia occurred with or without an increased protamine titration and vice versa Although these two changes were frequently associated they appeared to be independent phenomena From these facts it is obvious that random use of toluidine blue and/or protamine will lead to random results The nature of the abnormal bleeding which responds to these two substances is not entirely clear Though the antiheparin nature of the substances suggests that the bleeding tendency observed results from a heparin like substance in the blood this conclusion is not entirely warranted because these substances also react with other mildly anticoagulant substances not closely related to heparin for instance nucleic acid Specific conclusion as to the nature of the deranged clotting mechanism must therefore be deferred

[Until further experience by others in the difficult field of evaluating the effect of therapeutic agents on clinical bleeding has accumulated suspended judgment should be maintained about the clinical usefulness of protamine and toluidine blue —Ed]

COAGULATION DEFECTS

A period of very rapid development in the study of the physiology and pathology of coagulation defects is apparent from a survey of the literature On the one hand, studies of the processes of blood coagulation in as undisturbed an environment as possible (e g silicone coated glas ware) are being made and indicate the essential participation of platelets described in articles in the preceding chapter On the other hand isolation and purification of specific components of the plasma are yielding informative results as in the first article below Both types of investigation which may be termed physiologic and biochemical respectively appear to be conducive to progress —Eds

Serum Ac Globulin Formation from Plasma Ac Globulin, Role in Blood Coagulation Partial Purification, Properties, and Quantitative Determination Work on prothrombin purification has shown that thromboplastin and calcium ions activate purified prothrombin less rapidly than prothrombin in native plasma The ea e with which laboratory manipulations destroy prothrombin activity first suggested an additional fact ond co

hemophilia is deficiency of the precursor substance of prothrombin A small amount of thrombin in a hemophiliac permits normal coagulation time Determination of prothrombin consumed in coagulation of hemophilic blood is therefore a more reliable guide to the severity of the defect

Coagulation time in hypoprothrombinemia is relatively little prolonged until drastic reduction occurs For this reason determination of coagulation time is valueless for establishing a hemorrhagic condition in hypothrombinemia In afibrinogenemia blood is incoagulable Coagulability is restored by addition of a small amount of fibrinogen Since heparin increases coagulation time the test is valuable in controlling the therapeutic action of this drug

[This article should be carefully studied in the original —Eds]

The next article is an admirable clinical description based on extensive experience of hemophilia and its treatment —Eds

Hemophilia Clinical Study of 40 Patients Charles S Davidson Robert D Epstein George F Miller and F H L Taylor (Harvard Univ) report observations on clinical manifestations in and practical management of 40 patients with hemophilia all aged 12 or older followed during the last 10 years Twenty eight gave a family history of hemophilia and most of the others had inadequate information about their families Five patients died in the 10 years three of conditions unrelated to hemophilia One died when necrosis slough and sepsis followed apparently spontaneous massive hematoma in the left thigh muscles and one died of rapid submucosal pharyngeal and laryngeal hematoma formation which blocked the airway before help was available There were no deaths from acute blood loss the popularly supposed cause of death in hemophilia despite frequent tooth extractions and five relatively serious operative procedures For 36 patients time of the first hemorrhagic episode was known it varied from age 1 week to 13 years

(2) 1 4 97 119 F bru ry 1949

have been produced by interaction of prothrombin thromboplastin and calcium this thrombin is thought to convert plasma Ac globulin to serum Ac globulin Serum Ac globulin then facilitates rapid conversion of prothrombin to thrombin by co autocatalysis of the blood clotting mechanism

Serum Ac globulin has been obtained in concentrated form from bovine serum and from defibrinated oxalated bovine plasma Its chemical properties are identical with that of plasma Ac globulin It is stable in bovine serum and its activity can be measured quantitatively

Value and Limitations of Coagulation Time in Study of Hemorrhagic Diseases Because determination of blood coagulation time is subject to so much misinterpretation Armand J Quick Rene Honorato and Mario Stefanini[1] (Marquette Univ) standardized conditions under which they perform the Lee White test Important factors which must be controlled are temperature size of tube and nature and surface of the tube They perform the test at 37 C with the test tube in a hole in the cork of a water filled vacuum bottle Since size of the tube influences coagulation time serologic test tubes (13 × 100 mm with inside diameter 11 mm) were always used If the determination is not made immediately after the blood is drawn the latter is kept in a silicone lined syringe until used A tourniquet is applied just before puncture and if blood is not obtained immediately without trauma another vein is selected and a new puncture made The tube is gently tilted every 30 seconds and the end point taken as the moment no blood flows on tilting Normal range is 5 10 minutes

Coagulation time is prolonged in hemophilia hypoprothrombinemia afibrinogenemia and heparinemia The most prolonged coagulation times observed were in hemophiliacs but coagulation time may be normal This apparent discrepancy results from the fact that only a small amount of thrombin is necessary to convert fibrinogen to fibrin and cause blood coagulation The defect in

(1) Blood 3 1120 1129 O t be

due to paralytic ileus Low abdominal pain is the commonest abdominal emergency in hemophilia and may be due to bleeding into the colon wall or mesocolon or into or around the ileopsoas muscle With bleeding into the colonic wall or mesentery signs are usually those of partial bowel obstruction Retroperitoneal bleeding due to hemorrhage in or around the ileopsoas muscle is more common as is illustrated by the fact that 15 of the au

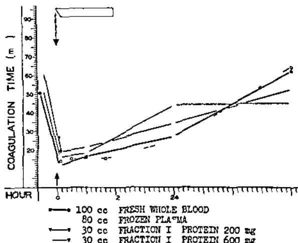


Fig 8 (C y t D d C S t l Bl J 4 97 119 F b y 1949)

thors patients had at least one episode of such hemorrhage When on the right side the pain may resemble that of acute appendicitis though it seldom begins in the epigastrium if the hematoma spreads distally and becomes palpable at Poupart s ligament or in the femoral canal differentiation from appendicitis is easier Differentiation from other intra abdominal conditions is facilitated if the femoral nerve is partially or completely involved by the hemorrhage

When acute blood loss of significant proportions oc

Bleeding into joints is the most frequent hemorrhagic episode in adult hemophiliacs knees and elbows being most frequently involved Acute hemarthroses frequently occur without known external trauma and are heralded by stiffness that soon becomes painful on joint movement and is followed within a few hours by swelling Usually blood remains confined to the joint and discoloration is not observed a fact which may cause acute hemarthroses to be mistaken for some other form of acute arthritis Repeated acute hemarthroses are followed by chronic and often deforming joint disturbance this occurred in 36 patients Spontaneous purpura is not characteristic of hemophilia When ecchymoses and hematomas occur they usually follow known trauma Almost 90 per cent of patients in this series had one or more episodes of hematuria Hematoma formation beneath mucosa of pharynx and larynx is one of the few emergencies in hemophilia and when a hemophiliac complains of sore throat loss of voice or both larynx and pharynx must immediately be carefully examined The patient is hospitalized and a tracheotomy kit kept at hand

All the common acute abdominal conditions occur in hemophilia and in addition purely hemorrhagic intra abdominal episodes occur which closely mimic and are more frequent than the usual acute abdominal emergencies Frequently differentiation is extremely difficult Upper abdominal pain (becoming progressively more severe and usually associated with nausea) vomiting and sometimes distention and tenderness or rigidity may occur last one or two days and then subside gradually To place the bleeding accurately in such episodes is usually difficult In some instances free fluid in the peritoneal cavity with signs of acute blood loss may become evident or a positive benzidine test may indicate bleeding into the gastrointestinal tract Pain in the midabdomen usually cramplike and resembling that of small bowel obstruction may occur in hemophilia and is probably due in most instances to bleeding into the bowel wall or mesentery Moderate distention and vomiting are the _ are

applied presents a much more serious and difficult problem of management

Because of lack of unanimity of opinion as to the best course to follow in hemophiliacs in whom acute surgical conditions develop Charles G Craddock Jr Leonard D Fenninger and Bradford Simmons[3] (Univ of Rochester) made a thorough search of the literature with the hope that definite conclusions might be reached This review revealed that reported instances of internal operative procedures in hemophiliacs require careful analysis Many cases are accompanied by data inadequate for diagnosis of hemophilia Mortality following internal surgery in established cases of hemophilia is relatively high In four previously reported cases in which diagnosis of hemophilia was unequivocal two patients died of hemorrhage after operation and two recovered The other 11 reports of internal surgical procedures in patients with bleeding tendencies were excluded from analysis because of inadequate basis for diagnosis of hemophilia If these 11 patients were included total number of recoveries from operation would be 11 with only four deaths a figure which the authors believe to be erroneously low They report a fatal case

Man 27 was hospitalized with typical symptoms of acute appendicitis He had first been seen at age 7 with a history of having bled profusely and bruised easily since early childhood Coagulation time of whole blood was four hours and diagnosis of hemophilia was made at that time Since then he had had numerous hospital admissions and clinic visits because of hemarthrosis hematuria and hemorrhage from the gums

Because of the hemophilia an attempt was made to treat him conservatively with penicillin sulfadiazine and hydration Coagulation time originally 60 minutes was reduced to 15 minute by administration of 0 4 Gm fraction I of Cohn (antihemophilic globulin) and 100 cc freshly prepared plasma After 10 hour observation during which leukocytosis fever and symptom increased it was decided to operate in view of normal coagulation time Great pains were taken to ligate or cauterize the smallest bleeding points Oozing from the appendical bed was satisfactorily controlled with Gelfoam pack No unusual bleeding was encountered Condition was good at

(3) A n. S g 1 8 888 903 N mbe 1948

curs in hemophilia whole blood is the therapy of choice since it not only provides antihemophilic activity but replaces loss of both red cell and plasma volume If whole blood is not necessary 100 250 cc plasma fresh or frozen is given for its antihemophilic properties Coagulation time is usually reduced to or near normal and the effect persists 6-12 hours (Fig 87) By blood plasma fractionation a preparation of human fibrinogen with antihemophilic activity for intravenous use is obtainable It not only lacks icterogenic properties but has the advantages over whole blood or plasma that maximal effect is achieved by a small amount and that it can be easily and quickly given However evidence suggests that refractoriness may more often follow repeated administration of antihemophilic globulin fraction than administration of blood or plasma Therefore therapeutic use of antihemophilic globulin fraction cannot be advised until this hazard has been eliminated

Although strict precautions must be taken by the hemophiliac against trauma this does not mean that he should live a sheltered inactive life Decrease in muscle size and tone from immobilization and disuse may be an important factor in initiating hemorrhage into muscles and neighboring tissues In local treatment of external bleeding the authors prefer thrombin as an anticoagulant Wounds should be cleaned with as little trauma as possible and edges approximated but not sutured unless absolutely necessary since each needle hole is another source of bleeding

Hemophilia Problem of Surgical Intervention for Accompanying Diseases Review of Literature, and Report of Case Surgical procedures in hemophiliacs carry the risk of fatal hemorrhage Site of trauma is probably the most important criterion of operability If the operative site is exposed so that local hemostasis pressure and hemostatic substances can be used chances of staunching the flow of blood are vastly increased Hemorrhage internally either spontaneous or secondary to trauma where local controlling measures cannot b nually

sode 100 150 cc plasma was given once or twice a day He indulged in many types of strenuous sport and for the fir t time did sustained remunerative work for 1½ years In the 20 months he had four bleeding episodes one followed severe trauma one accompanied infection and subsided after penicillin was administered and one occurred while he was on a month s holiday and treatment had lapsed

CASE 2—Man 28 was given 150 cc plasma three or four times a week for 17½ months and daily for 1/ months During this period for the fir t time in his life he was able to do remunerative work He drove 80 miles to and from the ho pital for treatments Open tenoplasties were done on both Achilles tendons during this period After an uneventful operation the wounds oozed despite relatively normal clotting time Oozing stopped when penicillin was given During pla ma treatment jaundice developed and persisted for four months It was attributed to homologous serum jaundice

CASE 3—Youth 17 was given 180 cc plasma three times a week for 13 months During this period he had his most sustained interval of uninterrupted school attendance and engaged in strenuou ports for the first time He had only three bleeding epi odes

CASE 4—Boy 8 given 100 cc plasma three times a week for 10 month was free of significant hemorrhagic episodes despite greatly increased physical activity

On the basis of experience with heparin the authors suggest that clotting time of hemophilic blood should be kept below 20 minutes The dosage and frequency of plasma administration used in the four patients was thought t represent the most practical program Though coagulation time often exceeded 20 minutes more frequent administration over long periods seemed impracticable It is hoped that antihemophilic plasma fractions will replace whole plasma in control of this disease

The therapeutic method is admittedly laborious and cumbersome It requires an efficient blood bank and the hemophiliac becomes tied to a hospital institution However patients may be scheduled to appear for treatment three times a week in the outpatient department and after 5 10 minutes of infusion are ready to leave

[Agai t the undoubted benefits of such a cont nuous therapeuti pr g am f r certain pat ents mu t be weighed the fact that many h mopl ili cs in whom for unknown reasons the bleed ng tendency slight get along without s gnificant bleeding ep sodes

the end of operation and histologic examination of the specimen confirmed clinical diagnosis During surgery the patient received 500 cc whole blood and one hour later was given 0.2 Gm Cohn fraction I and another 500 cc fresh blood

Despite the fact that coagulation time was kept almost entirely within normal limits the patient continued to lose blood into the peritoneal cavity and abdominal incision Distention severe enough to cause respiratory embarrassment necessitated removal of 1 200 cc bloody fluid from the abdomen the fourth postoperative day That evening respiratory embarrassment again became extreme Signs of bilateral pleural effusion were present After 150 cc bloody fluid had been removed by thoracentesis respiration ceased Autopsy revealed pulmonary edema bilateral hemothorax large blood clot in the appendical bed and tremendous hematoma of the abdominal wound

Persistence of hemorrhage in this patient despite normal coagulation time forces the conclusion that mere deficiency of antihemophilic globulin cannot be the sole abnormality of coagulation in hemophilia Time consumed by clot formation in the test tube is by no means an accurate measure of ability of hemostatic mechanisms to control blood loss

If site of bleeding cannot be treated with pressure application of hemostatic substances and other local measures chances of recovery from surgery are poor In view of unfortunate results of surgery in the case presented and the unconvincing reports of efficacy of major surgery in hemophiliacs in the literature conservative medical treatment seems the course of choice unless it becomes evident that death will ensue if surgery is not undertaken Dangers of hemorrhage outweigh dangers of peritonitis and fatal infection since means of controlling infection are at hand

Studies of Hemophilia Control of Hemophilia by Repeated Infusions of Normal Human Plasma Benjamin Alexander and Greta Landwehr[4] (Boston) report that they have kept four hemophiliacs almost symptom free for 12 20 months by giving them 100 180 cc plasma intravenously three times a week

Case 1 —Man 24 was given 150 cc plasma three times a week during most of 20 months During one hemorrhagic epi

(4) J A M A 138 174 179 Sept 18 1948

To exclude the possibility of a circulating anticoagulant blood was drawn from a normal donor and from the second patient Both specimens were citrated centrifuged and filtered Since addition of 0 1 ml patient s plasma to 2 ml normal blood did not change clotting time of nine minutes presence of an anticoagulant in the patient s plasma was ruled out

Addition of normal plasma to hemophilic blood accelerated coagulation time Under the same conditions 0 1 ml normal citrated plasma similarly accelerated clotting when added to 2 ml patient s blood When hemophilic plasma was added to the patient s blood no change in coagulation time occurred It was reasoned that normal plasma contains a substance which is absent or deficient in the blood of hemophiliacs and of the patient It is not known whether the deficient factor is the same in both

Tiselius protein fractionation revealed definite abnormality in alpha globulins in one patient and evidence suggesting abnormalities in the second It is thought possible that an acquired change in plasma protein pattern might be the basis of the coagulation defect in these patients The defect seemed similar to that in hemophilia

[In these patients the possibility of an acquired defect of the plasma globulin factor characteristically deficient in hemophilia on a hereditary basis finds an analogy in the congenital and acquired instances of hypoprothrombinemia and hypofibrinogenemia The evidence that in contrast to normal plasma plasma of a classic male hemophiliac failed to shorten the coagulation time of the patient s blood strongly supports such an analogy It is also of interest that spontaneous bleeding into joints occurred in one patient since this is a manifestation almost exclusively confined to hemophilia —Eds]

Circulating Anticoagulant as a Cause of Hemorrhagic Diathesis in Man. C Lockard Conley Howard K Rathbun William I Morse II and James E Robinson Jr[6] (Johns Hopkins Univ) report three cases

Case 1—Man 67 was hospitalized for hematuria He had never before had a bleeding tendency and there was no familial bleeding tendency Genitourinary study revealed no cause for bleeding Clotting time of whole blood was 68 minutes and of recalcified plasma 12 minutes (normal 2 minutes) Bleeding

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6 Bull Johns Hopkins Hosp 83 288 296 Oct be 194

for long periods Refractoriness to coagulation promoting effects of plasma would not have been observed in th patients studied because of the short interval between plasma infusions It would be of inter est to test for this situation after an interval of two to three weeks —Eds]

Hemophilia Like Disease in Women Report of Two Cases is made by James S Hewlett and Russell L Ha den (Cleveland Clinic) and so adds to the small number of such cases now reported

CASE 1—Woman 40 was hospitalized because of hemor rhages under skin and mucosae for six months There was no family history of bleeding for at least two generations Physi cal examination revealed no other abnormality Tourniquet test was negative platelet count 620 000 coagulation time 1 hour and 56 minutes coagulation time of recalcified plasma 21 29 minutes and bleeding clot retraction and prothrombin time were normal Fibrinogen value was 490 mg per cent and calcium value 9 4 mg per cent Red cell count was 3 100 000 white count 7 000 and hemoglobin value 9 3 Gm

CASE 2—Woman 33 was hospitalized because of hemor rhage under the skin into joints and from the nose for a month No familial hemorrhagic tendency was found Physical examination revealed no other abnormality tourniquet test was negative platelet count 430 000 coagulation time 2 hours and 45 minutes coagulation time of recalcified plasma 10 25 minutes bleeding clot retraction and prothrombin time ap proximately normal blood calcium value 10 mg per cent red cell count 4 940 000 white cell count 7 300 and hemoglobin value 12 5 Gm

Coagulation was reduced to 1½ hours by administration of 250 ml lyophilized plasma

Reviews of 600 hemophilic families in one series and 78 in another failed to reveal a single instance of the disease among females Isolated cases have however been described In these two patients the disease resem bled hemophilia clinically and was accompanied by pro longed coagulation time which is an outstanding charac teristic of hemophilia The defect in coagulation time of recalcified plasma which Quick considers pathognomonic for hemophilia was present in both patients Administra tion of normal citrated plasma accelerated coagulation time in one patient in a manner similar to that expected in hemophilia

(5) J Lab & Clin M d 34 151 157 Februry 1949

addition of thromboplastin Two patients plasma gave a normal response Clotting time of the third was prolonged *it could not be determined* whether the anticoagulant was antithromboplastic or whether it inhibited prothrombin activation

The authors suspect that such disturbances are not rare They suggest the desirability of anticoagulant assays on blood of patients with prolonged clotting time

Fibrinolysis has an obvious but as yet not fully explored relation to hemorrhagic conditions Thus in occasional clinical instances of shock from hemorrhage surgery or obstetric delivery hemorrhage difficult or impossible to control by usual means has been encountered *It has been noted that the blood clots formed in vitro* from samples of blood from such patients promptly redissolve Hypoprothrombinemia may also be present On the other hand there is evidence to suggest that fibrinolysis accelerates blood coagulation in vitro by an increase in plasma thromboplastin Perhaps *this action is ordinarily the physiologically dominant effect of a* small increase of fibrinolysis Fibrinolysis is authoritatively discussed in the following article which should also be read in the original —Ed

Fibrinolysis Its Mechanism and Significance Fibrinolysis the dissolution of blood clots has been studied for more than 100 years R G Macfarlane and Rosemary Biggs[7] (Radcliffe Infirm Oxford England) attempted to assemble the relevant information and relate it to their own observations

The first step in elucidation of fibrinolysis was the discovery that serum with chloroform added to it had the power of *digesting gelatin and casein* This activity was inhibited by addition of untreated serum It was then found *that the proteolytic enzyme* was confined *to* the globulin fraction and the factor which inhibited the enzyme was confined *to* the albumin fraction of serum

Other experimenters found that fibrin was lysed rapidly when brought into contact with culture filtrates of certain strains of streptococci Plasma of patients who had recovered from streptococcic infections resisted such fibrinolysis Pure fibrin resisted such fibrinolysis but when small quantities of serum globulin were added fibrinolysis proceeded rapidly It was postulated that a

(7) Blood 1 1167 1187 Oct 1945

time prothrombin time platelet count capillary fragility and plasma fibrinogen concentration were normal

CASE 2 —Man 39 was hospitalized for abdominal pain and weight loss of three months duration He had had no evidence of bleeding except two recent episodes of hemoptysis There was no family history of bleeding tendency He had been treated for syphilis five years before and his serologic reaction remained positive Two years earlier he had been reported to have a heart murmur and chronic glomerulonephritis Urinalysis revealed many red cells and albumin There were apical systolic and presystolic murmurs and splenomegaly Hemoptysis and abdominal pain recurred during hospitalization Clotting time of whole blood was 60 minutes and of recalcified plasma 7½ minutes Prothrombin time was 30 second (normal 16 20) Platelet count bleeding time capillary fragility and plasma fibrinogen concentration were normal

CASE 3 —Hemophiliac 38 had a blood clotting time of 5 hours and recalcified plasma clotting time of 17 minutes Prothrombin time platelet count bleeding time and capillary fragility were normal He had received numerous transfusions

The plasma of each of these three patients prolonged the clotting time of normal human blood to which it was added To determine if the anticoagulant was heparin or some related substance the effect of toluidine blue and of protamine was tested Clotting time was unaffected

Analyses failed to reveal proteolytic enzymes or proteolytic enzyme inhibitors in the plasma of any of these patients No precipitins against normal plasma or Cohn s fraction I were found in the serum of the hemophiliac Dialysis against physiologic saline solution failed to destroy the plasma s anticoagulant activity

Subsequent tests were designed to determine the phase of blood coagulation in which the anticoagulant exerted its effect Absence of antithrombic activity was demonstrated by the fact that clotting times were normal when oxalated plasma from each patient was mixed with thrombin solution Two patients plasma made prothrombin free by treatment with barium sulfate did not alter prothrombin time when added to normal plasma but that of the third prolonged the prothrombin time Antithromboplastic activity of plasma was estimated by determining the clotting time of platelet free on

removed from patients recently operated on showed fibrin webs which disappeared in 24 hours Further observation by Macfarlane and Biggs revealed that fibrinolysis occurred even before operation in anxious patients It could also be produced by exercise Since all these conditions are accompanied by epinephrine secretion it was speculated that epinephrine release might be associated with initiation of fibrinolysis In vitro epinephrine does not cause the development of fibrinolysis Judging from the effects of the injection of epinephrine in certain pathologic states the resulting fibrinolysis is independent of the functions of the adrenal cortex spleen pancreas and liver but lymphoid tissue may be involved

Plasmin is thought to be active in resorption of fibrin formed in all inflammation including pneumonia in disintegration of thrombi and in dissolution of clots in the endometrium during menstruation In chloroform poisoning there is demonstrable fall in serum fibrinogen It is postulated that plasmin functions in blood coagulation as one of the enzymes necessary for conversion of prothrombin precursors to their more active forms Plasmin may be the substance responsible for lowering of serum albumin concentration in Selye s alarm reaction Plasmin may be associated with release of histamine in anaphylaxis

The hemorrhagic d athesis observed i patie its with multiple myeloma (pla m ma) has been especially emphasized by American auth or The sugge tion of more than a coincidental relation between the hyperglobul nemia commonly found in this d sease and the bleed g tendency s enhanced by the observat ons reported in the next a ticle —Eds

Two Interesting Syndromes with Hyperglobulinemia (Purpura Hyperglobulinemia and Macroglobulinemia) Jan Waldenstrom[9] (Upsala Sweden) observed four women with chronic purpura which did not fit into any of the hitherto described categories of purpura In two the purpura had been known for 14 and 16 years in a third (who had had biopsy verification of Boeck s sarcoid 11 years earlier) the purpura had been known to

(8 S hw med. W h sch 8 9 7 9 8 Sept. 5 1948

lytic factor in serum globulin was necessary to sensitize fibrin to the action of the bacterial enzyme and that this lytic factor was identical with the proteolytic factor activated by chloroform

Christensen and MacLeod suggested that the name plasmin be given to the proteolytic enzyme of plasma to replace the terms serum trypsin serum protease serum tryptase fibrinolysin and thrombolysin The inactive

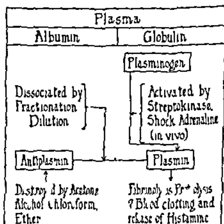


Fig 88—Diagrammatic representation of the activation of plasmin and its effects (Courtesy of Macfarlane R G and Biggs R Blood 3 1167 1187 October 1948)

precursor of plasmin is termed plasminogen The streptococcic filtrate factor previously called fibrinolysin is called streptokinase and the antibody developed by patients recovering from streptococcic infection antistreptokinase The inhibitor of plasmin found in plasma is called antiplasmin (Fig 88)

It was next necessary to find out what initiates the process of fibrinolysis Since traumatic shock had existed in all cases in which fibrinolysis had been demonstrated Macfarlane investigated the blood of patients undergoing surgical operations A fibrin web in normal blood samples was found to remain for weeks ... od

1 000 000 instead of the usual 150 000 It was not identical with the high molecular weight globulin found in small amounts in normal serum and which is associated with blood group The increased globulin value recalls myeloma but there was no clinical evidence of this disease Furthermore ultracentrifuge studies showed the abnormal protein of the two syndromes to be different To distinguish this new syndrome Waldenstrom has coined the term macroglobulinemia

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THE KIDNEY

In this sect on are included articles on the physiology and clinical a pects of renal function and its derangement Interest cont nues in the practical management of anem a wh ch develops in patient with pr marily normal renal function frequently in the form of the so called lower nephron synd ome The development of the artificial kidney for the purpose of treating such patients promises to be of more interest in throwing light on the nature of urem a than in the pra tical management of such pati nts provided mi guided efforts to force a diuresis are avoided during the period of dimini hed urinary output —Eds

Can Vascular Shunting Be Induced in Kidney by Vasoactive Drugs? Trueta demonstrated renal vascular shunts which bypass the cortex and are thought to be related to arterial hypertension These experiments were conducted on rabbits subjected to crushing of limbs large doses of epinephrine etc The present investigation was undertaken by Francois C Reubi and Henry A Schroeder[9] (Washington Univ) to determine whether similar phenomena occur in man and in dogs under normal or pathologic circumstances

It has previously been assumed that at least in normal subject nearly all blood goes first through glomeruli before reaching peritubular capillaries Experiments reported here are based on the assumption that opening or closing of anastomotic channels between arterie and veins would be reflected by relative changes in renal extraction of para aminohippurate (PAH) and/or man

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9) J Cl I st g t on 8 114 1 3 J y 1949

exist for at least 8 years Purpura in the fourth patient followed recent polyarthritis now healed All had episodes of petechiae on the extremities but no large ecchymoses All had elevated *sedimentation rates* Vigorous use of the arms elicited petechiae Mucosal bleeding was not seen There was no thrombopenia or increase in bleeding or coagulation time Mechanical evaluation of capillary resistance has not been considered because of the many sources of error

Besides purpura the other cardinal symptom of the syndrome is hyperglobulinemia Repeated examinations over a number of years consistently showed more globulin than albumin with *total protein up to 9 7 Gm* per cent Electrophoresis showed the increase to be due to gamma globulin Origin of the purpura is unknown it may be connected with the increase in globulin

Five men and one woman presented the *second* syndrome All were over age 60 The presenting complaints were fatigue shortness of breath pallor and in some nosebleeds Mucosal bleeding was common but there was no purpura The *only* characteristic physical finding was lymph node enlargement Microscopic examination of excised nodes showed only diffuse hyperplasia or reticulosis There were normochromic anemia normal or slightly diminished thrombocyte count and normal or slightly elevated white blood cell count Sternal puncture revealed normal marrow or some increase in small mononuclear cells This clinical syndrome might have been termed aleukemic lymphadenopathy were it not for the elevated sedimentation rate (up to 150 mm) attributable to marked elevation in globulin The highest value for globulin in the blood was 10 8 Gm per cent This protein had a rapid gel reaction and when the serum was dropped into distilled water the globulin precipitated as a white material readily soluble in physiologic saline solution In three patients electrophoresis indicated that the abnormal globulin was of the gamma group in three others of the beta group Ultracentrifuge studies showed the abnormal globulin to have a molecular weight of

Transfers of Potassium in Renal Insufficiency Elevated serum potassium levels have frequently and lowered serum potassium levels have occasionally been reported in patients with renal insufficiency Toxicity of of high concentrations of potassium on the cardiac conduction system is well established and is thought to be a frequent cause of death in uremic animals Elevation of extracellular potassium concentration is suggested as the fatal factor J Russell Elkinton Robert Tarail and John P Peters[1] (Yale Univ) attempted to determine incidence of hyperpotassemia and hypopotassemia in patients with severe renal insufficiency and to determine causes of these electrolyte abnormalities

In nine months 51 patients were found with nonprotein nitrogen concentrations above 100 mg per cent In 26 one or more measurements of serum potassium were made Serum potassium concentration was over 5 5 m Eq /L in more than half these patients Abnormally low potassium concentrations were found in four Serum potassium level rose as renal insufficiency progressed but had no quantitative relationship to elevation of nonprotein nitrogen In at least one patient serum potassium values fell as death approached

Serum potassium concentration was above 6 6 m Eq L only in patients who had produced less than 250 cc urine in the preceding 24 hours [If generally true a very practical clinical point --Eds] Periods of oliguria or anuria were not invariably followed by elevation of serum potassium level however

In three of five patients whose serum potassium concentration reached levels above 7 4 m Eq /L small amounts of potassium ingested in food exceeded urinary potassium output and the difference or positive balance was equal to part or all of the increase in extracellular potassium In patients with serum potassium concentrations under 6 5 m Eq L potassium intake was negligible Transfer of potassium from cellular to extra

(1) J Cl I g t on 28 378 388 M h 1949

nitol oxygen utilization or both [because mannitol is excreted by glomerular filtration PAH by tubules and work requiring oxygen is exclusively performed by renal tubule cells —Eds] Specifically arteriovenous anastomoses between relatively large vessels short circuiting both glomeruli and tubules might be expected to decrease PAH and mannitol extractions and renal arteriovenous differences Shunts supplying tubules bypassing glomeruli might be expected to decrease mannitol extraction alone and direct communications between efferent glomerular arterioles and renal veins bypassing peritubular capillaries might be expected to decrease PAH extraction slightly decrease oxygen differences and have no effect on mannitol extraction

PAH mannitol and oxygen content and hematocrit value in renal venous and peripheral or renal arterial blood before and after injection of epinephrine histamine or pentothal* were determined in eight hypertensive and six normotensive patients and in 15 dogs Maximal decrease in PAH extraction by kidneys of patients after subcutaneous injection of epinephrine or histamine was 11 4 per cent dog experiments were inconclusive Arteriovenous oxygen differences after injection of epinephrine were increased in two and decreased in three human subjects In dogs there was a consistent difference in oxygen capacity hematocrit value and plasma protein content between renal arterial and renal venous blood the latter being more concentrated This difference was increased by epinephrine The authors suggest that this loss of fluid from renal blood may have occurred through renal lymphatic vessels or other vascular channels bypassing the renal vein

It is concluded from these experiments that large intermittent renal shunts cannot be elicited in man by physiologic doses or in dogs by larger doses of epinephrine Even in subjects with essential hypertension histamine or epinephrine produced relatively small and inconsistent changes which could be ascribed to presence of shunts

in the extracellular space The artificial kidney and peritoneal and small intestine lavage are worthy of further investigation to determine their ability favorably to alter electrolyte balance in the presence of anuria

Potassium Deficiency and Role of Kidney in Its Production were studied by Robert Tarail and J Russell Elkinton (Yale Univ) It has been recognized that depression of potassium concentration in serum may reflect a concomitant deficiency of potassium in body cells However significant alterations in cellular content of potassium may occur without much change in amount and concentration of potassium in extracellular fluid and serum Therefore levels of serum potassium may but do not necessarily reflect state of cellular potassium

Six adult patients five of whom had conditions involving extensive losses of fluids from the gastrointestinal tract were studied All were being sustained wholly or in part by parenteral administration of fluids Potassium was administered in daily doses of 0 7 3 7 m Eq /kg Three normal subjects on diets isocaloric with usual daily intake of the six patients were given 4 4 3 2 and 0 m Eq potassium/kg as controls Daily exchanges of electrolytes and nitrogen were measured In order to differentiate at least to some extent between transfers of potassium which are associated with cellular anabolism or catabolism and those which are not a relationship of potassium to nitrogen of 2 4 m Eq to 1 Gm was assumed thus permitting determination of movements of potassium in excess of nitrogen

All six patients retained administered potassium in the cellular phase in excess of nitrogen in amounts varying from 1 2 to 4 6 m Eq /kg As control subjects did not this retention presumably indicates a pre existing cellular deficit of the ion Magnitude of the deficit was not defined by extent of retention in each patient however since only one patient received potassium long enough to show that maximal retention had been reached Cellular deficits of potassium as demonstrated by reten

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cellular spaces took place in most patients and in only two did the cells take up potassium

Storage of potassium by cells did not appear to be directly correlated with intake of carbohydrate or insulin Electrocardiograms on four patients with serum potassium concentrations above 7 4 m Eq /L showed toxic effects of potassium in all These patients died suddenly and in one an electrocardiogram within a few seconds of death showed widespread disorganization and prolongation of the QRS complex

It was thought that defective glomerular filtration was the principal factor limiting potassium excretion It is concluded that hyperpotassemia is common in renal insufficiency Extracellular potassium concentration is thought to depend on the volume of extracellular fluid potassium intake loss of potassium by the kidney and other routes chiefly the gastrointestinal tract and on the net transfer of potassium between extracellular fluid and intracellular spaces Though parenteral fluid administration may diminish extracellular potassium concentration experiments with animals have shown that expansion of extracellular volume may lead to transfer of some potassium from the cells It is thought that diminished potassium concentration in occasional patients results from losses of the ion from urine and gastrointestinal tract Since tubular resorption of potassium is more or less independent of tubular resorption of water diuresis may result in concentration of potassium in the body Use of calcium to counteract effects of increased concentrations of potassium has not been thoroughly investigated Use of glucose and insulin reported by others to diminish potassium concentration had no significant effect in the authors patients but was not given a thorough trial Likewise infusion of hypertonic sodium chloride given because of the possibility that increased concentration of potassium in the extracellular space is the result of low concentration of sodium there was ineffectual in one of the authors patients and their data reveal no evidence of diminished sodium chloride concentration

Food Protein Consumption in Glomerulonephritis Effect on Proteinuria and Concentration of Serum Protein Edward C Persike and T Addis[3] (Stanford Univ) administered varying amounts of dietary protein to two patients in the degenerative stage of glomerular nephritis Both were excreting large quantities of protein in urine both had low concentrations of serum protein and both were edematous The first patient was studied for four weeks and was given daily 0 5 Gm protein/kg the first week 1 5 Gm /kg the second week 2 5 Gm /kg the third week and 0 2 Gm /kg the fourth week The second patient was studied for three weeks and was not given the diet containing 2 5 Gm protein/kg because it was considered too risky in view of nitrogen retention

In both cases alterations in amount of food protein consumed were followed by parallel changes in quantity of protein excreted in urine When dietary protein was increased proteinuria was augmented Similarly decrease in dietary protein diminished proteinuria Concentration of serum protein was unaltered while patients received nutritionally adequate amounts of protein Raising protein intake above 0 5 Gm protein/kg did not increase serum protein concentration However serum protein concentration decreased during the week that protein intake was reduced to 0 2 Gm /kg

Dietary treatment of glomerulonephritis has evoked much discussion The observations recorded here demonstrate that a higher than adequate protein intake does not elevate serum protein concentration and that it increases rate of excretion of protein in urine Increased proteinuria is accompanied by increased urea clearance and is thought by some to be harmless to the kidneys It may however further tax protein resorptive ability of tubular cells this capacity already having been exceeded Furthermore added burden may be placed on the mechanism for production of plasma proteins which also may be conceived to be functioning imperfectly under stress When more dietary protein is consumed than can be

(3) A h I t M 1 81 61 6 2 M y 1948

tion of the ion were usually but not always associated with a low concentration of serum potassium (four patients with gastrointestinal fluid loss had abnormally low levels of serum potassium)

Major factor in development of potassium deficits in these patients appeared to be continued excretion of potassium by the kidney during times of restricted ingestion of the ion During the period of low potassium intake more potassium was lost in urine than in gastrointestinal fluid In four patients during such periods quantity in urine was greater than it was during periods when intakes were high and concentrations in serum normal In three patients who were in nitrogen equilibrium conditions were optimal for renal conservation of potassium Yet rates of potassium excretion in these patients were 28 27 and 5 5 m Eq/day and the lowest concentration ratio of urine to serum (U/P) was 1 0 Under these conditions and in these patients there was no direct evidence of active tubular reabsorption of potassium against a concentration gradient

The authors conclude that adult patients deprived of potassium by gastrointestinal disorders retain significant amounts of administered potassium and that this retention probably indicates cellular deficit of the ion Such deficits are frequently but not always associated with abnormally low concentrations of serum potassium The kidney in normal subjects as well as in depleted patients under conditions of maximal need for conservation has a limited minimal rate of excretion of the potassium ion This continued excretion by the kidneys is an important factor in producing potassium deficiency

These observations offer no evidence that correction of deficit of cellular potassium directly benefits the patient However the rationale of replacement therapy has been to restore the patient to a normal chemical state It appears reasonable therefore to attempt to put replacement of intracellular electrolytes on the same successful basis as that which has been achieved for constituents of extracellular fluid

In no case did kidney function improve after transfusion and in two kidney dysfunction was strikingly aggravated with decrease in urea clearance value and alkali reserve and increase in urea retention Salvesen concludes that the anemia of chronic kidney insufficiency plays no part in lowering kidney function and its treatment by repeated blood transfusions is of little benefit Since alkali reserve decreased as hemoglobin content increased in two patients with severe acidosis it is suggested that transfusion may even be dangerous in nephritic patients with kidney insufficiency and severe acidosis

[Although the author refers to the anemia in these patients as severe hemoglobin values ranged from 48 to 75 per cent averaging 61 per cent Perhaps in patients with more severe anemia improvement would have been noted

The six articles concluding this chapter are concerned with the treatment of anuria or uremia If of a presumably temporary nature as in the acute anuria of lower nephron nephrosis the importance of avoiding errors of commission made through ignorance of the physiologic problems involved cannot be too strongly emphasized The patient must not be drowned from pulmonary edema induced by parenteral administration of excessive amounts of saline and glucose As pointed out by Strauss in the first article before the advent of parenteral fluid administration many patients with complete anuria survived for from three to four weeks Today if the patient's chances are not jeopardized by misapplication of modern methods and if the cause of the anuria is potentially reversible spontaneous recovery will usually occur This strikingly limits the occasions on which use of dialysis from the peritoneum or by means of the artificial kidney will be indicated —Eds]

Acute Renal Insufficiency Due to Lower Nephron Nephrosis Maurice B Strauss[5] (Framingham Mass) presents evidence suggesting that neither nitrogen retention nor acidosis is responsible for the usual fatal outcome Death is often due to pulmonary edema or in its absence to potassium intoxication Available data indicate that man may survive without renal function for four or more weeks if excessive quantities of fluids are not administered parenterally and that the tubular lesion is often reparable with spontaneous diuresis to be expected within three weeks if the patient can be kept alive this long

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[5] New England J Med. 39 693 700 N 4 1948

utilized the excess is deaminated to form urea and this increases the burden on the kidneys In view of these considerations it seems not only logical but necessary to prescribe not more than the minimum adequate amount of dietary protein as a rule not over 0 5 Gm /kg daily plus an increment equal to the amount of protein lost in urine

[Periods of observation of only a week in length are too short to permit the conclusion that an increase in protein consumed will fail to increase plasma proteins This argument applies with even more force to a potential deficit in body proteins the existence of which can be inferred with some certainty from the fact that in one patient a protein intake of 0 2 Gm./kg caused a fall in plasma protein within a week The fact that an increase in protein intake caused an increase in proteinuria does not prove that no body protein was synthesized by this procedure unless the increased output of urinary protein plus urinary nonprotein nitrogen (for which no data are given) quantitatively accounted for the increased loss or catabolism of the increased dietary protein In Case 1 when the protein intake was increased from 0 5 to 2 5 Gm /kg /day a five fold increase the urinary protein increased from an average of about 11 to about 23 Gm /day or only a twofold increase It is entirely possible that some of the dietary protein thus unaccounted for by a quantitative increase in urinary protein was incorporated into body proteins including renal cell proteins Thus in giving a low protein diet to nephritic patients one must still choose empirically between the disadvantages of potential injury to the kidney of a somewhat increased proteinuria and the possible injury of general tissue protein deficits —Eds]

Effect of Blood Transfusions on Kidney Function in Chronic Nephritis with Anemia It would seem reasonable physiologically that kidney function which is so dependent on a high minute volume and function of the tubules which depends on a high oxygen supply would be unfavorably influenced by anemia Harald A Salvesen[4] (Oslo) investigated this point in nine patients with chronic nephritis and one patient with polycystic kidneys All patients had severe kidney insufficiency and moderately severe anemia All were given blood transfusion until hemoglobin and red cells were normal or nearly so Urea clearance test of Moller McIntosh and Van Slyke which is regarded as the best measure of total kidney function was performed in all patients before and after transfusion

(4) Acta med Sca In 131 337 341 1948

Treatment of Acute Renal Insufficiency is outlined by E E Muirhead and J M Hill[6] (Baylor Hosp Dallas) Acute bilateral renal damage with acute renal insufficiency is variously designated renal anoxia syndrome lower nephron nephrosis and hemoglobinuric nephrosis Mortality has been reported to be 80 90 per cent The condition may result from traumatic operative or obstetric hemorrhage incompatible blood transfusion crush syndrome blackwater fever burns severe alkalosis carbon tetrachloride poisoning heat stroke or sulfonamide intoxication severe pyrogenic reaction and transurethral prostatectomy with water hemolysis

Most patients with this condition die within eight days Patients who survive this interval frequently recover It is of great importance to maintain the patient until regeneration of renal tubules occurs between the eighth and twelfth day The authors believe that much of the high mortality can be ascribed to therapy

Clinical course of the condition may be divided into three phases Phase 1 lasts a few hours at most and consists of shock during which the renal damage is sustained Phase 2 is that of renal insufficiency and is characterized by oliguria and azotemia Urine specific gravity soon becomes low and output of solids in urine is slight During the first few days proteinuria may be prominent and urine may contain red cells white cells and casts Blood urea concentration may reach 80 100 mg per cent during the first two days and attain a peak of 300–400 mg in five to seven days At the same time there is a tendency toward acidosis with fall in plasma bicarbonate concentration Serum sodium and chloride concentrations are lowered despite substantial intake of sodium bicarbonate Serum potassium concentration may be moderately elevated early in the course of the condition but the authors have seldom found it very high Significant lowering of calcium concentration has not been observed in uncomplicated cases Hemoglobinemia and hemoglobinuria recede during the first 36 hours

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[6] Gynec & Obst 87 445 456 Octob 1948

A review of the numerous treatments proposed for this condition fails to show that any one speeds the appearance of spontaneous diuresis Strauss recommends a regimen used at Cushing Veterans Administration Hospital which consists essentially in replacement of water loss and in supplying 100 Gm dextrose daily This it is believed may in many cases help the patient to survive long enough to recover spontaneously

If shock or dehydration is present in the initial phase of the syndrome whole blood plasma or saline solution is used The second phase of treatment begins when urine volume is greatly diminished or anuria has occurred 750 cc of 15 per cent glucose in distilled water is given daily by slow intravenous injection with every precaution to avoid venous thrombosis Nothing is given by mouth If there is significant vomiting the amount is measured and that much physiologic saline solution is added to the daily infusion of dextrose If acidosis becomes clinically manifest as well as being evident on laboratory examination 1 L of M/6 sodium lactate is given Electrocardiograms are made at least every other day to observe changes indicating excess of potassium If this occurs it may be possible to combat it by inserting a modified Miller Abbott tube into the small intestine and perfusing into the proximal jejunum a slightly hypertonic potassium free electrolyte and dextrose solution which is withdrawn from the distal ileum where its potassium content should be in equilibrium with the blood plasma Any loss of sodium is replaced intravenously by potassium free Ringer lactate or M/6 sodium lactate solution

When diuresis appears in the second or third week the third phase of treatment is begun It consists in administration of a volume of water sufficient to make up for total urine volume plus 1 000 cc for insensible and any other losses plus the amount of sodium chloride found in the preceding day s urine Frequently during the phase of diuresis moderate to severe anemia is noted This is treated by transfusion of carefully

anuric patients Edward L Pratt[7] (Harvard Univ) believes that death from anuria is usually due to disorganization of the structure of the internal environment and not to accumulation of urea or hypothetic toxin Therefore the rational approach is to preserve normal volume and composition of body fluids

In presence of anuria and in absence of intake of food and fluids volume of body water is progressively reduced through insensible expenditure by way of lungs and skin and concentrations of body fluid electrolytes rise (unless losses occur in vomitus and in diarrheal stools) Owing to consumption of body protein quantity of protein oxidation products in body fluids increases and their concentrations therefore rise more extensively than those of electrolytes It is also evident that intake of protein adds to the accumulation of nitrogenous end products On the other hand if water intake larger than insensible expenditure is provided concentrations of electrolytes fall below their physiologic values

These considerations lead to a simple rationale of treatment Sufficient water should be provided to replace insensible expenditure and glucose should be given in sufficient quantity to obtain maximal sparing of body protein If concentrations of the large components of extracellular electrolyte structure have been lowered by losses from the gastrointestinal tract or from the skin in hot weather they should be rebuilt by provision of appropriate quantities of sodium chloride and sodium bicarbonate If concentrations are elevated a deficit of water is indicated which should be repaired Guiding data required are daily measurements of body weight and less frequent determinations of the concentrations of sodium chloride and bicarbonate in serum

As soon as diagnosis of an intrarenal type of anuria is established an accurate measurement of body weight should be made and a blood sample drawn for immediate determination of concentrations of bicarbonate chloride

(7) Am J Dis Child 76 14 5 July 1948

Patients without added complications particularly water or water salt excess and acidosis frequently remain mentally clear despite severe oliguria for five to eight days

Phase 3 is that of diuresis and constitutes the early period of recovery Diuresis is copious and may be prominently associated with excretion of salt In the few instances in which kidney function has been studied for long periods after an episode of acute renal insufficiency renal function has returned to near normal in two to four months

Grossly the kidneys increase in weight because of abnormally large water content The greatest brunt of the injury is sustained by the distal segment of the nephron the glomeruli remaining intact

Treatment during phase 1 consists of transfusion of compatible blood to offset hypotension During phase 2 a near normal state of hydration may be maintained by water intake equal to urinary volume plus the estimated insensible water loss This varies between 800 and 2 000 cc depending on environment fever etc Acidosis is checked by periodic administration of sodium bicarbonate usually by mouth Plasma bicarbonate concentration should be maintained within lower limits of normal To do this it is usually necessary to administer about 4 Gm sodium bicarbonate daily Diet should include about 1 calorie/cc as fluid intake during the early oliguric period Intake of soft and general hospital diets is encouraged as early as possible and vitamins B and C are administered orally During phase 3 excessive water and salt loss must be replaced

Treatment of Anuria Management of Patients with Intrarenal Lesions Abrupt development of anuria as the result of intrarenal lesions in patients with previously adequate renal function is encountered with increasing frequency because reactions from transfusions of incompatible blood crush injuries and sulfonamide therapy produce this type of anuria As a result of study of nine

large amounts of fluid is the best treatment for lower nephron nephrosis and in support of their contention report the survival of five of six patients treated in this manner

Lower nephron nephrosis is severe oliguria or anuria following an initial shocklike picture in which renal insufficiency occurs with subsequent uremia and usually death Autopsies have revealed that kidneys in this condition are edematous and that the principal kidney lesion is degeneration and necrosis of cells of the ascending loop of Henle and the descending convoluted tubules The condition most often occurs after crushing injuries to muscle transfusions with incompatible blood and sulfonamide intoxication but has occurred in many other conditions

Management of lower nephron nephrosis is controversial Most urologists practice operative intervention Ureteropelvic lavage especially for removal of sulfonamide crystals has been widely used and kidney decapsulation has often been performed Decapsulation is recommended by Peters who believes that the chief factor responsible for prolonged oliguria is increased intrarenal pressure On the other hand it has been claimed that decapsulation cuts sympathetic constrictor nerve fibers to the kidney and thus increases blood flow Thorn has contended that patients reported to have benefited by decapsulation would have improved without surgery and that the apparent benefit of surgery resulted because it was performed at a period when in the natural course of the disease recovery might have been expected

In contrast to Thorn and others the authors believe that fluids should be administered in large quantities to patients with lower nephron nephrosis chiefly to dilute toxic products accumulated because of diminished kidney excretion They carefully induce edema during the period of oliguria as a method of diluting toxic products The aim is to keep the patient alive until tubules recover sufficiently which they usually do 8 10 days after onset Optimal nutrition is assured by adequate calorie and

and sodium in serum Until the direction and magnitude of the derangement already present in body fluids is ascertained the patient should receive nothing orally or parenterally lest inappropriate unguided treatment aggravate the existing disturbance Sufficient fluids should be allowed each day to keep body weight constant This allowance of water to replace imperceptible losses is modified as indicated by serum concentration of sodium elevation in sodium concentration demands replenishment of water deficit in addition to provision of water for insensible expenditure whereas a lowered concentration indicates limitation of water intake until normal value for sodium has been roughly restored In the event of reduction in concentrations of serum electrolytes appropriate amounts of sodium chloride and bicarbonate should be administered to restore the concentrations of each to satisfactory values The only food substance required is glucose of which enough should be provided to furnish infants 30-60 calories/kg./day Older children and adults are given 100 200 Gm glucose/day irrespective of body weight Glucose can generally be given by mouth

Practicability and efficacy of this plan of therapy is demonstrated by the fact that one of the author s nine patients survived 11 days of complete anuria another was maintained for 18 days in which urine volume averaged only 40 cc daily and five patients survived anuria of 1-4 days duration Only two patients died In both autopsy revealed irreversible renal lesions

In most instances any substitute for the kidney such as dialysis from an artificial membrane or from the peritoneum involves risk to the patient and provides no more certain preservation of the integrity of body fluids than that obtainable with the principles discussed in this report

Management of Lower Nephron Nephrosis Report of Six Cases William S Hoffman and Daniel Marshall[8] (Hektoen Inst Chicago) believe that administration of

(8) Arch. Int M d 83 249 270 Ma h 1949

large amounts of fluid is the best treatment for lower nephron nephrosis and in support of their contention report the survival of five of six patients treated in this manner

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protein intake amelioration of anemia by blood transfusion and provision of water soluble vitamins Electrolyte and hydrogen ion concentrations are kept as nearly normal as possible Administration of specific electrolytes to correct specific electrolyte abnormalities is sometimes necessary The authors have had no experience with use of the artificial kidney peritoneal infusion or intestinal lavage

During the first 24 36 hours after oliguria has been recognized 2 3 L isotonic sodium chloride solution containing glucose and 1 L of M/6 sodium lactate are administered intravenously Fluid administration on subsequent days is based on chemical and clinical findings If severe acidosis continues sodium bicarbonate is injected intravenously with other fluids Taking food by mouth usually in the form of a full soft diet supplemented with vitamins B and C is encouraged Calcium gluconate 20-40 cc of a 10 per cent solution is often injected to combat tetany phosphate and guanidine retention After the first day most of the authors six patients were given 2 L sodium chloride solution in 5 per cent glucose and 600 cc of M/6 sodium lactate solution daily If edema fluid was accumulating rapidly and concentrations of sodium and chloride remained low 500 cc of 2 per cent sodium chloride solution was administered slowly When the patient ate well and did not vomit parenteral administration of fluid was replaced by oral administration and the quantity of salts desired was given with food During periods in which the patient was unable to take fluids by mouth 30 50 Gm amino acids was administered intravenously During the entire period of oliguria penicillin was given in doses of 20 000 unit every three hours As soon as urinary output reached 500 cc daily administration of sodium chloride by mouth and vein was discontinued and the patient was treated as though he had cardiac edema

Shock had occurred in each of the authors patients except possibly one who had carbon tetrachloride poisoning Oliguria persisted for 5 13 days A had

edema during the period of oliguria but it disappeared rapidly with diuresis The usual symptoms of uremia were slow to develop and vomiting was less severe than was expected Serum calcium concentrations tended to be low and serum phosphate concentrations high Serum protein concentrations were low Serum potassium values rose considerably only in the one fatal case Serum chloride and sodium concentrations which were lower than normal despite the presence of edema were not elevated by administration of isotonic sodium chloride solution but were elevated by administration of 2 per cent sodium chloride solution The tendency of serum nonprotein nitrogen concentration to level off in later days of oliguria in these patients despite continued intake of protein was attributed to expansion of the extracellular fluid from fluid administration Relative mildness of uremic symptoms was attributed to this expansion

[The deliberate induction of edema for the purpose of diluting the accumulating intoxication products is certainly opposed to the policy of the authors of the preceding articles Our impression would be that it was fortunate that under these circumstances only one patient developed terminal hydrothorax and edema of the lungs The subject is doubtless controversial but until further evidence is forthcoming we prefer to employ a regimen that attempts primarily to maintain homeostasis for measurable quantities such as electrolytes and water rather than for unknown toxin —Eds]

Artificial Kidney Clinical Experiences of Dialytic Treatment of Uremia Nils Alwall Lembit Norviit and A M Steins[9] (Univ of Lund) summarize their experience with use of an artificial kidney in 12 uremic patients The artificial kidney used consisted of 10-11 m Cellophane tubing providing a dialyzing area of about 6 500 sq cm Tubing is wrapped around a cylinder of wire netting and surrounded by a mantle of the same material The authors experiences showed the practicability of this apparatus and helped them perfect a technic for using it Lasting therapeutic results are not claimed because in many patients studied kidney disease was too advanced to permit survival

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Cause of uremia in one case was ureteral obstruction from cancer in one hypertension with nephrosclerosis in two cystic kidneys in four acute subacute nephritis and in four chronic nephritis In all patients nonprotein nitrogen was over 200 mg per cent when treatment was instituted

Nonprotein nitrogen concentration was substantially reduced in all patients in whom the artificial kidney was used Simultaneously serum concentration of uric acid xanthoprotein and indican fell Total base remained unchanged in patients in whom it was normal at start of treatment and increased in those in whom it had been low Bicarbonate values when low at onset of treatment became normal and when normal before treatment showed no change

It was possible to continue treatment for 20 hours or more without noticeable inconvenience to the patient As much as 200 L blood was dialyzed in one treatment Blood pressure changes were insignificant

Large doses of heparin were used in the beginning but in later cases initial dose was 100 mg and not more than 300 mg was used during 10 12 hours dialysis Construction of the authors dialyzer was calculated to reduce risk of blood coagulation Blood did not as in Kolff s apparatus pass rotating couplings a rotating cylinder or a Beck tube pump length of Cellophane tubing was only one quarter that in Kolff s apparatus and blood was pressed in a thin layer through the tubing

In an amazingly short time after initiation of treatment with the artificial kidney stupor nausea and vomiting of uremia diminished

Adjusted hydrostatic pressure prevented inflow of water from the saline solution to the blood and thus eliminated the possibility of causing edema Lowering the dialyzer 70 cm below the patient and adding up to 7 5 per cent glucose to the solution were ineffective in removing enough fluid from the patient to make the procedure of practical value for relief of edema Though lung edema sometimes appeared during o ately

after treatment it was thought that this complication would have occurred in the normal course of the uremia and could not be blamed on use of the artificial kidney No increased strain on the heart was apparent

Temporary chills occurred 1½ 2 hours after initiation of treatment but were not considered of great significance Contrary to Kolff s experience hemolysis presented no great problem

Kidney Substitutes in Uremia Use of Kolff's Dialyzer in Two Cases is described by R A Palmer and P S Rutherford[1] (Vancouver B C) The artificial kidney used consists of a Cellophane tube 50 ft long wound spirally around a wooden drum which rotates at 25 30 rpm through a water bath containing essential electrolytes and glucose A special hollow axle and rotating coupling at each end permits continuous blood flow during drum rotation All parts in contact with blood are kept sterile but the Cellophane is a sufficient barrier to bacteria so that sterilization of water bath and other parts of the apparatus is unnecessary Temperature of the bath is maintained by a heating element Bubbles are trapped before blood is returned to the patient Transfusion of 500 800 cc blood is given to compensate for amount of blood in the apparatus Dialyzing surface of about 24 000 sq cm is comparable to that provided by a normal kidney The water bath contains 0 57 per cent sodium chloride 0 04 per cent potassium chloride 0 2 per cent sodium bicarbonate and 2 25 per cent glucose in 100 L tap water

The authors experiences confirmed the observations of others that this apparatus effectively reduces retention of nitrogenous and other substances Technical application of the method is not difficult In two instances venous flow did not keep up with arterial flow probably because the saphenous vein used was too small or was in spasm Although the apparatus constitutes an arteriovenous shunt none of the characteristic effects on cardiovascular function were noticed except slight tachycardia

(1)—C d M A J 60 61 266 M h 1949

Since essential electrolytes are readily dialyzable they tend toward equilibrium with the water bath and are easily controlled except for calcium which must be replaced occasionally during treatment Although the authors patients were not weighed before and after dialysis both appeared more hydremic after treatment than before

Control of water balance depends on maintaining sodium concentration at the lowest safe level and use of some substance in the bath which will act as a colloid Repeated observations of serum chloride level and carbon dioxide combining power during dialysis are necessary The problem of providing suitable colloid for the water bath has not yet been sufficiently studied Sodium chloride concentration of 0 57 per cent is considered safe The authors first patient died of pulmonary edema A sodium chloride concentration of 0 6 per cent was used in the water bath for this patient Heparin in doses of 300-400 mg should be used at the start of dialysis and in 50 100 mg doses during dialysis as indicated by blood coagulation time Blood sugar rose to 1 000 mg per cent in one patient at a time when drowsiness and irritability of uremia were clearing and was partially controlled by a small dose of insulin

The authors recommend use of ureteral irrigation or sympathetic block in patients with anuria If after these procedures are done renal function does not return in four to six days it is suggested that a dialyzer be used It is thought to be more adequate than methods involving portions of the gastrointestinal tract or pleura and to avoid the disadvantages of peritoneal lavage i e peritonitis ileus and difficulty in maintaining adequate flow The authors two cases follow

Case 1—Woman 23 became anuric during shock from premature separation of the placenta and massive hemorrhage which required two blood transfusions A renal biopsy specimen taken eight days after delivery at the time of bilateral renal decapsulation showed cortical necrosis Gastric suction was maintained and she was given 2 000 3 000 cc of 5 per cent glucose intravenously and almost daily bl usions

Dialysis was performed on the tenth and thirteenth day. In the first dialysis 3,000 cc. blood was dialyzed every hour for eight hours and in the second 6,000-9,000 cc./hour for six hours. Temporarily after each treatment he showed symptomatic improvement and nonprotein nitrogen value fell from 140 to 118 mg. per cent. Urine flow appeared after the second dialysis and increased, but the patient died of pulmonary edema four days after the second dialysis. During dialysis there were hypocalcemia and hyperglycemia.

CASE 2.—Woman, 36, was hospitalized in shock from hemorrhage induced by abortion. She was anuric for nine days despite a splanchnic block. Blood dialysis for six hours with blood flow of [illegible]0-110 cc. minute resulted in fall of nonprotein nitrogen from 200 to 126 mg. per cent, rapidly increasing urine output, and survival.

THE HEART *and* BLOOD VESSELS

TINSLEY R. HARRISON M.D

PART IV

THE HEART AND BLOOD VESSELS

Perhaps the mo t significant and certainly the most exciting new developments are the preliminary reports (from Mayo Clinic and el ewhere) suggesting that compound E (wh ch is a product of the adrenal gland and has nothing to do with vitamin E) and ACTH (the adren corticotrophic hormone of the anterior pitu tary) may have a beneficial effect on acute rheumatic fever It will probably be some years before these substances become generally available Meanwhile it should be empha ized that there is no convincing evi dence of the value of vitamin E in the therapy of cardiovascular disease

In selecting articles for abstracting this year special emphasis has been placed on those dealing with treatment and disturbances of the peripheral circulat on Although the literature is filled with reports mostly of small importance on electrocard ography rela tively few have been abstracted There is a wide pread tendency to put too much emphasi on this method and to base far reaching judgments on minor electrocardiographi changes It eem to be the history of most valuable tools that they inevitably undergo a period of misuse and abu e before their true place in th medical armamentar um i established

—TINSLEY R HARRISON

DIAGNOSIS OF HEART DISEASE

The phys cian is l kely to be bewildered by the ncreas ng number of relatively new methods available for study of the heart These include balli tocardiography angiocardiography cardiac catheter ization roentgenokymography and electrokymography in addition to the newer technics in electrocardiography These various tech nics not only a e of value in research but in the hands of those with special experience are of value in determin ng the presence and the type of heart disease Neverthele s for the average phys cian and for the specialist n the field of heart d sease physical exam na tion of the patient (not of the heart alone) i st ll the mo t valu able objective procedu e in solut on of ca d ovascular problems Even more important is a careful and thorough h tory which provides the best ndex to the heart s funct onal capac ty and hen e to prognosis and often prov des the sole means of d agnosing the earlier stages of d stu bances of the coronary circulat on

In view of these con derations it may not be inappropriate to

begin this chapter with articles stressing the importance of information obtained by the unaided senses —Ed

Auscultation of the Heart is believed by Samuel A Levine[1] (Harvard Univ) to be a more valuable procedure than is generally recognized He recommends listening only to the first heart sound for several seconds then only to the second sound then only to the systolic interval and finally to the diastolic interval The first heart sound is assumed to be entirely valvular in origin When excessive tissue is interposed between heart and stethoscope both heart sounds are diminished but alteration of first sound intensity without simultaneous change in intensity of the second sound may be of great significance Intensity of the first sound may be increased by conditions which increase velocity of blood flow—anemia hyperthyroidism exercise infection and emotion—and it is increased in mitral stenosis

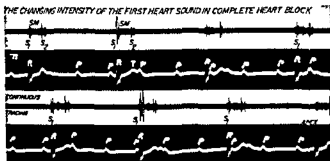
Levine conducted studies recently on patients with alterations in intensity of the first sound not attributable to any of these conditions This study was based on the belief that loudness of the first sound depends on exact position of auriculoventricular valves at the instant ventricles contract It is assumed that the first sound is louder if valves are deep in the ventricles and wide apart and fainter when valves are higher up and closer together Normally ventricles contract 0 16-0 18 second after auricles contract If auriculoventricular conduction time is prolonged intensity of the first heart sound is diminished A case is cited of a man aged 50 who had fainted several times but whose physical examination revealed no abnormalities until diminution of the first heart sound was detected Prolongation of P R interval was suspected and was verified by ECG and later experience proved that he had had Adams Stokes syndrome

Because in complete dissociation of auricles and ventricles the interval between auricular and ventricular contraction varies from beat to beat intensity of the

(1) B t He t J 10 213 2 8 Octobe 1948

first sound varies in this condition In Figure 89 simultaneous tracings of phonocardiograms and electrocardiograms of a patient with complete auriculoventricular block show the loudest first heart sound to occur simultaneously with the shortest P R intervals

Sometimes it is clinically valuable to remember that in paroxysmal ventricular tachycardia auricular rhythm is independent of ventricular rhythm and is accompanied by variations in intensity of the first sound in paroxysmal auricular tachycardia auriculoventricular conduc-



Fg 89—M 33 w th Ad m St k d L d t fi t d (S) m w th y h t P R t I Int ty f y t l m m (SM) m t t (C t y t Le S A B t H t J 10 213 2 8 O t b 1948)

tion time is constant and there is no variation in intensity of this sound This distinction and failure to influence ventricular tachycardia by vagal stimulation help to distinguish between the two

Auricular flutter is accompanied by constant auriculoventricular conduction time and therefore first heart sounds are of constant intensity in auricular fibrillation first heart sound may vary in intensity because of variations in P R interval Brief exercise frequently converts irregular rhythm to a regular one in patients with flutter but in patients with fibrillation rhythm continues irregular after exercise After vagal stimulation such as holding a deep breath the rate slows and then becomes fast

Steinberg[3] (New York Hosp) were able to demonstrate pericarditis with effusion in four patients by injecting radiopaque substances into the cardiac chambers by cardiac catheterization Chest x rays showed the cardiac silhouette to be much smaller than the pericardial Figures 90 and 91 demonstrate the difference in radiopacity of the heart and pericardial fluid in two patients with pericardial effusion studied by angiocardiography In two of the four patients presence of pericardial



F g 90 (l ft) —Cont t film t two sec ds R ght s b la n om t p o a a a d ght at um a v l d Not pe cardial fl d h d w dj nt t ght at um.
F g 91 (ght) —Cont t film at l se o ds P lmona y l ft at m left nt i l nd ao ta are op c fi d Shad w of p ard l fl d see bey d l ft nt cle
(C urt y of W ll m R G d St nb g I Am J R tg nol 61 41 44 J ry 1949)

effusion was not suspected clinically and was not suggested by routine x ray studies None of the patients had any serious reactions during or after angiocardiography

Results of Anatomicoclinical Study of 171 Cases of Apical Systolic Murmur C Callebaut[4] (Paris) made 414 observations of various cardiopathies with autopsy and found 171 apical systolic murmurs (40 per cent) that could be divided into two large etiologic groups

1 Rheumatic cardiopathies 98 cases (57 per cent of apical systolic murmurs or 24 per cent of cardiac cases studied) The systolic murmurs were due to mitral in

(3) Am J Roe tg l 61 41 44 J ry 1949
(4) A h d m l du oeu 41 645 653 A mbe

sufficiency and occurred as organic murmurs from valvular lesion in the classic sense or as functional murmurs from myocardial dilatation or alteration

2 Various cardiopathies including especially the arteriosclerotic and senile hearts mainly in patients between 51 and 70 73 cases (43 per cent of apical systolic murmurs or 18 per cent of cardiac cases studied) Twenty seven patients had hypertension (systolic pressure 180 mm or over) 14 myocardial infarct (3 also had hypertension) 11 angina pectoris (4 also had hypertension) 8 syphilitic aortitis (5 had hypertension) and 13 senile heart with more or less cardiac insufficiency (1 with hypertension)

Explanation of the systolic murmur in these 73 cases was far from clear Clinically only one patient had systolic vibration 53 murmurs were soft and of the 20 which were more intense 11 were holosystolic 30 murmurs spread beyond the apex and a gallop was heard in two thirds of the cases In most date of appearance of the murmur was vague and only rarely could correct information be obtained after myocardial infarction

Autopsy revealed that in 58 cases the papillary muscle myocardium or chordae tendineae were involved In 24 of 41 cases with normal mitral orifice the left ventricular was dilated The papillary muscles were involved in 10 myocardium in 13 myocardium and papillae in 15 myocardium and papillae with thick chordae in 1 and papillae with shortened chordae in 2 In one case the mitral orifice was slightly narrowed and papillae were involved with thick chordae Mitral orifice was dilated in 16 cases in 12 of which the left ventricular cavity was dilated The papillae were involved in three myocardium in six myocardium and papillae in five and myocardium and papillae with thick chordae in two

In 15 cases papillary muscles and chordae were not affected The mitral orifice was normal in nine in six of which the left ventricular cavity was dilated The mitral orifice was dilated in six in five of which the

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Fig 90 (left) —C t t film t two ond Right b la an m at upe o ve a c a d right t m e sual d Not p ca d l fl d h dow d c t t ght t um.
Fig 91 (right) —C t t film t 12 nds P lmon y e l ft at m left v t i l a d ta r op fi d Sh d w f p r cardial fl d see b y d l ft v t cl
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(4) A h d n l d coe 41 645 653 N mb r

a corregated patch of localized intimal thickening thought to result from trauma produced by a jet of blood striking the wall after passing through the zone of aortic narrowing This lesion is important because its avascularity may prevent adequate healing if sutures are placed through it or if it is left in place a saccular aneurysm may develop in this region The authors do not consider coarctation the result of overgrowth of the ductus arteriosus into the aorta The intima which is involved most markedly in coarctation is not concerned in closure of the ductus arteriosus It is thought that the zone of intimal thickening increases during the lifetime of the patient with coarctation

Death usually results from congestive heart failure rupture of the aorta intravascular bacterial infection or intracranial lesion

Collateral Circulation—Jesse E Edwards O Theron Clagett Russell L Drake and Norman A Christensen[7] point out that the subclavian arteries through communication of their branches play the paramount role in carrying blood from the part of the aorta above the coarctation to the part below Intercostal arteries are the most important anastomotic bridges because of their communications with the aorta below the coarctation and with the internal mammary musculophrenic superior epigastric anterior spinal and lateral thoracic arteries and the descending branch of the transverse cervical artery Vessels about the scapula which communicate with intercostal arteries contribute materially

Dilated intercostal arteries notch the ribs on the inferior and anterior aspects of the main body of the rib at the point where it joins that part of the rib which forms the wall of the costal groove

Clinical Features Review of 96 Cases—Norman A Christensen and Edgar A Hines Jr[8] report that from 1925 to 1947 119 patients at the Clinic were diagnosed as having coarctation of the aorta Records of 96 were suit

( ) P oc Staff Meet M Cl 23 333 339 J ly 21 1948
(8) Ib d pp 339 34

The apical systolic murmur in these arteriosclerotic or aged hearts is nearly always related to myocardial alterations of the left ventricle In 4 per cent (3 of 73 cases) the heart seems to be normal

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CONGENITAL HEART DISEASE

The rapid advances in therapy and in diagnosis of congenital heart disease are illustrated by the articles abstracted in this chapter The time has passed when the physician can be content with a diagnosis of congenital heart disease of the cyanotic type When doubt exists after the usual clinical and roentgenologic studies have been made such special investigations as angiocardiography or *cardiac catheterization must be employed It is probable* that future advances with the comparatively simple procedure of electrokymography will make this method of increasing value in the diagnosis of the less common congenital disorders

It should be stressed that congenital malformations of the heart which are not associated with cyanosis and which are amenable to surgical cure (patent ductus arteriosus coarctation of the aorta and double aorta arch) are usually diagnosed readily by the ordinary clinical and roentgenologic procedures —Ed

Symposium on Coarctation of Aorta—*Historical Review*—Norman A Christensen[5] points out that though coarctation of the aorta has been diagnosed for 100 years only in the past 10 years has animal research been carried out on the surgical aspects of this condition and only in the past 5 years has successful surgical reconstruction been done in man

Pathologic Considerations—Jesse E Edwards *Norman A Christensen O Theron Clagett and John R* McDonald[6] describe the configuration of coarctation of the aorta as resembling two cones with the apexes placed end to end The usual location of this condition is the vicinity of the aortic insertion of the ligamentum arteriosum At times a zone of narrowing extends for several centimeters When the interior of the aorta is examined a diaphragm like structure is found to cross the lumen A small opening in the diaphragm constitutes the aortic lumen at the involved level Just distal to the stricture is

(5) P c St ff M t *May Clin 23 3 2 3 4 July 21 1948*
(6) Ib I pp 3 4 33

means of a venous occlusion plethysmograph with a compensating spirometer recorder found only insignificant abnormalities in the resting blood flow of the extremities of patients with coarctation of the aorta as compared with the flow in the corresponding extremities of the same number of normal persons under identical conditions Studies made before and after excision of the coarctate portion in some cases of coarctation however showed a slight average decrease in blood flow to the arms and an increase in that to the legs after operation

Pre and Postoperative Studies of Intraradial and Intrafemoral Pressures in Patients with Coarctation of Aorta — George E Brown Jr O Theron Clagett Howard B Burchell and Earl H Wood found that delayed onset of the femoral pulse wave was eliminated after operation Values for arterial blood pressure however were changed little by operation when the aorta was anastomosed to the subclavian artery but much more striking changes occurred when there was end to end anastomosis of the aorta

Surgical Treatment —O Theron Clagett[3] reports results in 21 patients aged 7 34 The best time for operation is during the second decade Before this period the aorta is not large enough for satisfactory anastomosis moreover it is not yet known whether the aorta after anastomosis will increase in size as normal growth occurs After age 20 on the other hand there may be considerable vascular damage if coarctation is severe Older patients have not been denied operation when they demanded it

In eight patients it was impossible to do an end to end anastomosis because of the length of the segment which would have had to be resected or because of the location of the stricture In these patients the aorta was anastomosed to the left subclavian artery Results were not good In 13 patients end to end anastomosis was done There were five deaths in the entire group Two patients

(2) Proc Staff Meet Mayo Cl 23 35 358 July 21 1948
(3) Ibid pp 359 360

able for evaluation Important clinical features in diagnosis are differences in arterial pulsations and blood pressure of the upper and lower extremities murmurs collateral circulation rib notching on x rays and characteristic direct intra arterial radial and femoral arterial pulsations and blood pressure differences Of the 96 patients 76 were males High blood pressure was the most frequent presenting complaint but symptoms were varied and not characteristic Pulsations in the abdominal aorta and in the legs were feeble or not palpable in 84 per cent of patients and were reduced in all but two of the others Pulsations in the neck and upper extremities were frequently described as bounding Hypertension in the upper extremities was found in 89 per cent Collateral circulation was recorded in 74 patients Most frequently scapular and infrascapular regions were involved Murmurs were heard in 94 per cent the most characteristic being a loud precordial systolic murmur maximal over the base of the heart In 20 per cent there were diastolic murmurs in this region A small number of patients had x ray and electrocardiographic evidence of myocardial damage Except in complicated cases renal function was normal

Value of Roentgenologic Diagnosis—David G Pugh[9] states that notching of the ribs is almost pathognomonic of coarctation of the aorta About one fourth of patients with coarctation however exhibit no definite x ray evidence of this condition Absence of this roentgen sign in children may be explained by the fact that collateral circulation has not yet developed and in adults it must be assumed that constriction of the aorta is not sufficient to necessitate development of large intercostal arteries In some patients x ray examination first calls attention to the condition

Studies on Blood Flow in Extremities Determinations before and after Excision of Coarctate Region—Khalil G Wakim Owen Slaughter and O Theron Clagett[1] by

(9) Proc Staff Meet Mayo Clin 23 343 347 July
(1) Ibid, pp 347 351

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(2) P oc St ff M t M y Cl 3 35 358 J ly 21 1948
(3) Ib 1 pp 359 360

died of heart failure postoperatively and three of separation of the anastomosis None of the last six patients have died Results are evaluated as satisfactory in 12 of the 16 patients who survived operation

Analysis of Malformations of Heart Amenable to Blalock-Taussig Operation is presented by Helen B Taussig[4] (Johns Hopkins Univ) Over all mortality for 350 operations on patients of all ages with all types of cardiac malformations and a clinical diagnosis of inadequate pulmonary blood flow was 19 per cent for a later group of 250 operations it was less than 10 per cent Among children aged 2 12 with tetralogy of Fallot on whom it was possible to use the subclavian artery operative mortality was less than 7 per cent Operative risk is considerably greater in persons with atypical malformations with pulmonary stenosis or atresia

Accurate diagnosis of atypical malformations is extremely difficult Patients with malformations other than tetralogy of Fallot who have been improved by operation include those with a cardiac contour similar to that of tetralogy of Fallot but with left axis deviation those with partial rotation of the heart on its axis and possibly those with pure pulmonary stenosis and an auricular septal defect

Six criteria are essential for successful completion of operation on a patient with any unusual malformation (1) Primary difficulty must be lack of adequate pulmonary blood flow Children so affected squat when tired Reduplication of the second sound is good evidence that both great vessels are functionally important A pure second sound suggests that functionally there is but one great vessel Pulmonary congestion or hemoptysis is strong presumptive evidence of adequate pulmonary blood flow (2) There must be a pulmonary artery to which the systemic artery can be anastomosed Persistent patency of the ductus arteriosus clearly indicates presence of a pulmonary artery In infants with adequate blood flow lungs are exceptionally clear roentgenograph

(4) Am Heart J 36 3 1 333 September 1948

ically while if collateral circulation develops via posterior mediastinal vessels hilar shadows become exaggerated Angiocardiography may aid in visualization of the pulmonary artery Finally it may be impossible to determine existence and size of pulmonary artery without thoracotomy (3) A systemic artery must be available for anastomosis (4) Difference in pressure between systemic and pulmonic circulation must be such that blood will flow from aorta to pulmonary artery Unless pulmonary atresia is present pulmonary pressure may be measured by catheterization of the heart and passage of the catheter into the pulmonary artery (5) Lung structure must be such that patient can survive collapse of one lung and occlusion of one pulmonary artery (6) Heart structure must be such that it can adjust to altered circulation

There are four primary considerations with regard to heart structure (1) Venous blood must be directed to systemic circulation for to benefit the patient unoxygenated blood must reach the lungs An overriding aorta or some other right to left shunt is essential to fulfil this condition Abnormally short circulation time arm to tongue of less than 10 seconds indicates clearly that venous blood has reached the aorta without passage through lungs Angiocardiography or catheterization will also demonstrate overriding aorta (2) Oxygenated blood must reach the aorta Size of aorta and degree of dextroposition determine the ease with which oxygenated blood from the left ventricle is directed to the aorta Accurate evaluation of this point preoperatively is enigmatic (3) Blood must circulate continuously at an accelerated rate With a single ventricle there is never difficulty in expulsion of blood from the common chamber into the aorta A gross defect in the auricular septum will present no difficulty If there is tricuspid atresia and only a small defect in the auricular septum expulsion of blood from right to left auricle may be difficult Left axis deviation in cyanotic patients may indicate tricuspid atresia defective development of the right ven

tricle and a small auricular septal defect Pulsation at the margin of a normal sized liver is strong presumptive evidence of tricuspid stenosis or atresia combined with an opening in the auricular septum so small that expulsion of blood from the right auricle is difficult (4) Cardiac reserve must allow the heart to carry the increased load placed on it by altered circulation Postoperative course is the best test of these factors Only 2 or 3 of 220 patients followed more than two years continued to show increase in heart size six months after operation In about 40 per cent of patients the operation has caused no demonstrable cardiac enlargement In about 30 per cent the heart enlarged during the first three weeks after operation but progressed no further Almost an equal number had an increase in heart size between discharge and return for the six month check up Thereafter enlargement ceased Enlargement occurring between three weeks and six months coincides with the period in which the patient first greatly increased his activity Follow up studies indicate that in most children anastomosis of the subclavian to the pulmonary artery is as beneficial as when the innominate artery is used and the load placed on the heart is lighter

Method of Increasing Lung Blood Supply in Cyanotic Congenital Heart Disease was devised by N R Barrett and Raymond Daley (St Thomas s Hosp London) To increase pulmonary blood supply in patients with tetralogy of Fallot two operations have been devised In the Blalock operation a systemic artery is anastomosed to one of the pulmonary arteries The second operation is incision of the stenosed pulmonary valve These operations cannot or should not be performed on all patients with tetralogy of Fallot In some pulmonary arteries are absent or too small to permit anastomosis Blalock s operation may be impossible if the aortic arch and the pulmonary artery are not close together The condition of some patients is so serious before operation that the surgeon may hesitate to embark on a prolonged

(5) Brit M J 1 699 70 Apr 23 1949

operation Conversely function may be altered so slightly that a long operation seems unjustifiable

It occurred to the authors that in such patients pulmonary blood flow might be increased by production of pleural adhesions to bring systemic blood to the pulmonary circulation Such collaterals have been found in patients born without pulmonary arteries in patients who have had artificial pneumothorax for long periods and in fact at thoracotomy in many patients with tetralogy of Fallot

In one child on whom the Blalock procedure was attempted a large number of pleural adhesions had to be dissected to free the aorta and the pulmonary artery The pulmonary artery was too small to permit anastomosis and the child died 20 minutes later Autopsy showed that the left pleural cavity was obliterated by adhesions and it was thought that death resulted from removal of collateral circulation present in these adhesions In another patient the Blalock procedure could not be performed because it was impossible to approximate the subclavian and pulmonary arteries The parents were told that nothing could be done Surprisingly the patient returned a few months later greatly improved and improvement was presumed to have resulted from creation of pleural adhesions at operation

With these experiences in mind the authors set out to create pleural adhesions in patients with tetralogy of Fallot The method involved removing the parietal pleura from the upper mediastinum from the dome of the pleura and from the upper half of the chest and dusting powdered asbestos onto the raw surfaces Another operation to improve circulation to the lungs entailed bringing the omentum into contact with the parietal pleura When the omentum was brought into the chest via holes in the diaphragm progressive diaphragmatic hernias were created so it was most practical to bring the omentum up into the chest via the rectus sheath immediately superficial to the muscle fibers of the transversus abdominis

Operations of this type were performed on six pa tients and judging by clinical signs such as improved exercise tolerance diminution of cyanosis and less fre quent squatting good results were achieved in two pa tients three others were considerably improved In only one patient were results poor Significant improvement occurred in three of four patients on whom details of resting oxygen saturation were obtained before and after operation In six patients oxygen capacity was meas ured before and after operation and in four there were significant decreases In another oxygen intake and carbon dioxide production changed from decidedly ab normal to normal Possibly the e results will be im proved after longer follow up periods

Atrioventricular Anastomosis Additional Valve A Rappaport J F Murray and L S Davies[6] (Univ of Toronto) created an artificial valve in dogs between the left auricle and left ventricle They hope that this opera tion will be of value in treatment of patients with steno sis or mitral valve insufficiency Operation was per formed on 13 dogs with only 1 death Success was achieved by reducing to econds the phase of operation during which the ventricle is open thus limiting blood loss to 50 150 cc

TECHNIC —Through an incision in the fourth intercostal space for the left auricular appendage or in the third inter costal space for the right the app ndage is visualized A curved clamp is placed at its base The appendage is joined to the myocardium of the adjacent ventricle by a row of mattress sutures and opened longitudinally along its borders so that two flaps joined at their tip result A thread is drawn through the two lateral incisions to be used later as a guide thread An incision 15 × 5 mm is made in the anterior ventricular wall A curved needle is introduced into the heart cavity 3 cm below the ventricle opening The guide thread is threaded into the curved needle and the latter is pulled out quickly drawing the appendage into the incision and ventricular cavity Anas tomosis is completed by mattress sutures uniting the anterior wall of the appendage to the edge of the ventricular incision

No regurgitation through the anastomosis was ob

(6) Proc Soc Exper B I & M d 69 345 348 No emf 1948

served After the clamp is opened blood from the atrium streams through the anastomosis and pulsates in rhythm with the atrium

Double Aortic Arch Report of Two Cases is made by Willis J Potts Stanley Gibson and Robert Rothwell[7] (Children s Memorial Hosp Chicago) Since establishment of a successful surgical treatment for double aortic



Fg 92—L t l film h w g ty ph gu (C t y f P t W J t l A h S g 57 233 A g t 1948

arch every pediatrician has been on the lookout for such cases The clinical picture is characteristic Laryngeal stridor and respiratory difficulty are usually the first symptoms and appear shortly after birth They may be mild or severe are often intermittent and may vary with the infant s position Respirations are usually rapid and noisy and even during sleep breathing is labored There may be wheezing and attacks of severe dyspnea are

(7) A h S g 57 7 33 A gu t 1948

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(6) Proc Soc Exper Biol & Med 69 345 348

Pathologic studies have shown that an ascending aortic arch in patients with this condition splits into two segments which encircle the esophagus and trachea and then reunite to form the descending aorta A vascular ring constricts esophagus and trachea (Fig 93)

Pure Congenital Pulmonary Stenosis and Idiopathic Congenital Dilatation of Pulmonary Artery David G Greene Eleanor deForest Baldwin Janet Sterling Baldwin Aaron Himmelstein Charles E Roh and Andre Cournand[8] (New York City) reviewed the literature on 68 cases of pure congenital pulmonary stenosis without abnormal shunts and 8 cases of pure congenital dilatation of the pulmonary artery and added 8 examples (4 of each) from their own records

Both conditions are characterized by enlargement of the pulmonary artery and systolic murmurs along the left sternal border survival to adulthood is possible When not associated with shunts they are not accompanied by cyanosis *Study of these cases suggests that the two* conditions may be differentiated by intensity of the pulmonic second sound usually accentuated in patients with dilatation of the pulmonary artery and usually diminished in pulmonary stenosis

Cardiac catheterization of the authors patients revealed a significant drop between systolic pressure in the right ventricle and that in the pulmonary artery It is reasoned that in pulmonary stenosis the narrow outlet causes hypertension in the right ventricle in dilatation of the pulmonary artery normal pressure becomes dissipated in the enlarged artery Pressure in the right ventricle differentiates the two conditions In differential diagnosis of enlargement of the pulmonary artery one must consider disease of the lung mitral stenosis auricular septal defect and patency of ductus arteriosus

Atrial Septal Defects are discussed by Thomas J Dry[9] During fetal life the septum which later is to close the foramen ovale is kept open by regurgitation of blood

(8) Am J M d 6 24 40 J y 1949
(9) M Cl N th Am 3 895 910 J ly 1948

frequently associated with cyanosis and suprasternal re traction Attacks of unconsciousness are not rare Re current respiratory infections keep the child in poor health and as he grows older a crowing nonproductive cough like the bark of a sea lion is characteristic Dysphagia is an equally distressing symptom At times feedings are taken without discomfort but most of the time feeding is a problem and regurgitation is likely to

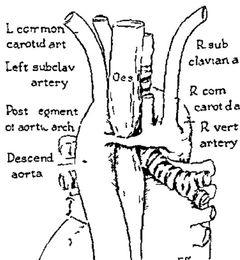


Fig 93—Obs rv t on t a t psy in c se of d bl aort c rch m i t 1 st t r s wed p te ly (Cou te y f P it W J t l A h s g 57 2 7 33 Aug t 1948)

set off an attack of coughing stridor and cyanosis Be cause of similarity of these symptoms to those associated with enlargement of the thymus these children have sometimes been given x ray therapy

Orally administered radiopaque substances show a concave defect in the esophagus produced by pressure of the abnormal vessel This defect is best seen in the lateral view (Fig 92) but may also be apparent in the anteroposterior view Bronchoscopic examination may show depression of the trachea just above the carina

with atrial septal defects many reach adult life with this abnormality Of Dry s 25 patients 5 died between age 1 and 7 and 2 lived into the third decade 4 into the fourth 2 into the fifth 5 into the sixth 4 into the seventh and 3 to the age of 70 or more

Incomplete Division of Atrioventricular Canal with Patent Interatrial Foramen Primum (Persistent Common Atrioventricular Ostium) H Milton Rogers (Mayo Found) and Jesse E Edwards[1] (Mayo Clinic) report five cases Case 2 is given here

Girl aged 5 months was hospitalized because of respiratory di tre s Cyanosis had been noted intermittently since birth and was precipitated by feeding or crying Development had been slow Examination revealed the facies hyperflexibility of the fingers and thick protruding tongue of mongolism pronounced cyanosis respiratory distress and fever There were bilateral pulmonary rales No cardiac murmur was heard Moderate anemia was present and an x ray revealed cardiac enlargement suggesting congenital cardiac disease The child died two days after admission

Autopsy observations in this case and in two others were similar Essential anomalies in each heart consisted of a defect in the lower portion of the interatrial eptum a defect in the superior aspect of the posterior region of the interventricular septum and failure of formation of the right and left halves of the atrioventricular canal The persistent single atrioventricular canal was guarded by one valve which wis common to both sides of the heart The large anterior cusp of this valve was composed of those elements which normally become the anterior halves of the septal cusp of the tricuspid valve and of the anterior or so called aortic cusp of the mitral valve Similarly the posterior cu p of the common atrioventricular valve was composed of tissue which normally is represented by the posterior halves of the septal cusp of the tricuspid valve and the aortic cusp of the mitral valve The lateral cusps of the common valve represented the anterior and posterior tricuspid and posterior mitral cusps

(1) Am H t J 36 8 54 J ly 1948

from the left to the right atrium As soon as pressure in the right atrium falls below that in the left the foramen ovale closes This event occurs when the pulmonary circulation begins to function in the newborn During the first year of life the foramen ovale is normally large enough to admit a probe and in about 20 per cent of persons this condition persists indefinitely but is ordinarily of no clinical importance When the atrial septum is so malformed that an opening persists after birth which permits a left to right shunt the right ventricle dilates and hypertrophies both atria enlarge and there is dilatation of the pulmonary artery and its main branches As long as the shunt is arteriovenous no cyanosis occurs

Review of 133 cases of all types of congenital heart disease at Mayo Clinic revealed 25 in which there was an atrial septal defect large enough to produce symptoms Eighteen of the patients were females Diagnosis was suggested by presence of basal systolic murmur accentuated pulmonic second sound occasionally accompanied by a soft diastolic murmur of pulmonary insufficiency enlargement of both atria right ventricle and pulmonary artery accentuated hilar pulsations and electrocardiographic evidence of right ventricular strain possibly with right bundle branch block Cardiac catheterization helps in differentiation of atrial septal defects from patent ductus arteriosus when the characteristic machinery murmur is not present and is of value in differentiating it from conditions that cause primary cor pulmonale or idiopathic dilatation of the pulmonary artery The commonest arrhythmia observed in patients with atrial septal defects was auricular fibrillation Other electrocardiographic findings suggesting presence of an atrial septal defect were right axis deviation large bifid P waves prolongation of the P R interval right bundle branch block and inversion of T waves in leads II and III The constitutional delicacy of patients with atrial septal defects has been stressed by various authors

Though sudden death sometimes occurs in patients

diagnostic problem is differentiation of this condition from tetralogy of Fallot (pulmonary stenosis ventricular septal defect hypertrophy of the right ventricle dextroposition of the aorta) and Eisenmenger s syndrome (identical with tetralogy of Fallot but with dilatation of the pulmonary artery instead of stenosis) All were characterized by marked clubbing cyanosis polycythemia possible survival to adulthood and loud systolic murmurs along the left sternal border

The survey suggests that the most valuable clue in differentiation is x ray appearance of the pulmonary artery The x ray picture of the heart in tetralogy of Fallot shows a concavity which replaces the usual prominence at the upper part of the left sternal border By contrast Eisenmenger s syndrome accentuates the shadow cast by the pulmonary artery and distends smaller branches of the pulmonary blood vessels Prominence of the pulmonary artery in x rays of patients with pulmonary stenosis and patent foramen ovale is intermediate between that found in the other two conditions Intensity of the second pulmonic sound is usually diminished by pulmonary stenosis and accentuated by dilatation of the pulmonary artery However the second aortic sound may be transmitted to the pulmonary area Murmur in patients with pulmonary stenosis and patency of the foramen ovale is usually maximal along the upper left sternal border whereas that of tetralogy of Fallot is maximal along the lower left sternal border possibly because it is mainly from ventricular rather than auricular septal defect Angiocardiography and cardiac catheterization have not been conducted on enough patients for differential diagnostic values to be firmly established

Since pulmonary stenosis with patent foramen ovale is amenable to the same type of surgery used in tetralogy of Fallot and Eisenmenger s syndrome is not it is important that Eisenmenger s syndrome and the syndrome being considered be differentiated Pulmonary stenosis with patent foramen ovale is a conspicuous exception to the rule that cyanotic congenital heart disease with di

Essential anomalies in the hearts in the other two cases consisted of a cleft in the anterior or so called aortic cusp of the mitral valve The septal cusp of the tricuspid valve was intact The tissue of the aortic cusp of the mitral valve and that of the septal cusp of the tri cuspid valve were continuous beneath the defect in the lower interatrial septal defect which was present in each of these hearts These two cases are considered to portray a lesser degree of the anomaly seen in the complete form in the first three cases

Study of these 5 cases and review of 50 reported in the literature revealed that the median age of patients at death was 10 months More than half the patients died before age 1 year Only five patients lived beyond age 30

The lesion acts essentially as does a simple inter atrial septal defect Enlargement of the right side of the heart and widening of the pulmonary artery orifice are common associated secondary lesions Cyanosis may be present at birth but is usually acquired When this mani festation develops it is a sign of failure of the right side of the heart pulmonary disease or both Cardiac murmurs usually systolic are frequently observed they occurred in 22 of 25 cases in which an adequate history was given as to this sign Mongolism is a relatively com mon associated condition in cases of incomplete division of the atrioventricular canal with patent interatrial foramen primum Bacterial endocarditis was observed in 3 of the 55 cases The anomalies are attributed to failure of fusion of the ventral and dorsal atrioventricu lar endocardial cushions in early embryonic life

Syndrome of Pulmonary Stenosis with Patent Fora men Ovale Arthur Selzer William H Carnes Charles A Noble Jr William H Higgins Jr and Robert O Holmes (San Francisco) analyzed data on two patients with pulmonary stenosis plus patent foramen ovale seen in their clinic and 27 reported in the literature in an attempt to establish criteria for diagnosis The usual

(2) Am J M 6 6 323 January 1949

congenital anomalies such as patent ductus arteriosus and patency of the interauricular or interventricular septa without appreciable shunt from right to left heart circulation time was relatively normal In congestive heart failure there was pronounced prolongation of circulation time

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RHEUMATIC HEART DISEASE

The two articles in this chapter illustrate the natural course and management of rheumatic heart disease Recent reports not yet available suggest that compound E (not vitamin E) may be of great value in treatment of acute rheumatic carditis The substance will probably not soon be on the market Drugs already available (and especially penicillin) appear to be very effective in preventing recurrences but are apparently useless (and possibly harmful) in treatment of the acute phase of the disease —Ed

First 10 Years of Rheumatic Infection in Childhood In 1946 and 1947 Rachel Ash[4] (Univ of Pennsylvania) made a survey of all patients whose primary rheumatic manifestations occurred while they were residents of Philadelphia County during 1923 37 Although many were followed for much longer periods the present study is limited to the first 10 years after the initial illness All children with a diagnosis of rheumatic infection were included irrespective of presence or absence of clinically recognizable heart disease

Diagnosis of mitral insufficiency was made when a persistent high pitched systolic blow at the apex was present Aortic insufficiency was diagnosed in the presence of a diastolic blow at the left or right of the midsternum Mitral stenosis was diagnosed only when there was a characteristic diastolic rumble to the right of the apex Usually the mitral diastolic rumble was accompanied by accentuation of the first mitral and second pulmonic sounds Most patients had definite evidence of cardiac enlargement

Of 537 children followed for 10 years after their initial attacks of rheumatic fever 219 had no clinical

(4) Am Heart J 36 89 97 July 1948

lated pulmonary arteries is unsuitable for surgical relief

The authors suspect that patients reported to have cyanosis from pulmonary stenosis without septal defects had *undetected septal defects*

Fluorescein Circulation Time in Normal and Pathologic Conditions in Infants and Children, Including Various Types of Congenital Malformations of Heart, is reported by Benjamin M Gasul John J Marino and Joseph R Christian[3] (Univ of Illinois) The circulation time is the measured interval between injection of a test substance into the circulation and its recognition by various methods Successful use of many of these substances depends on the patient s subjective response It is often necessary and desirable to use a substance with which one can accurately determine circulation time without depending on any subjective response Fluorescein seems to satisfy this requirement Sodium fluorescein is a nontoxic substance which when injected intravenously emits a brilliant green fluorescence when viewed under the long wave ultraviolet lamp

TECHNIC—The calculated dose of sodium fluorescein was approximately 0 7 cc per 10 lb body weight of a solution containing a dilution of 5 per cent sodium fluorescein in 5 per cent sodium bicarbonate The drug was injected rapidly into the antecubital vein in a darkened room with the ultraviolet lamp concentrated on the lips The time interval between beginning of *injection* and the *first appearance of a brilliant green* fluorescence of the mucous membranes of the mouth was measured with a stop watch.

The test was performed in 107 patients aged 15 days to 13 years 57 had demonstrable cardiac pathology and 50 no demonstrable cardiac disease In the normal noncardiac group circulation time from the neonatal period through 2 years varied from 5 to 8 5 seconds (average 6 5) *from* 3 years through 13 years it varied from 5 to 12 5 seconds (average 8 5) In congenital anomalies with an arteriovenous shunt definite shortening of circulation time was noted Thus in tetralogy of Fallot average circulation time was 3 7 seconds whereas in

(3) J Ped t. 34 460 4 4 Ap 1 1949

perature and sedimentation rate should be normal for one or two months before it can be assumed that rheumatic activity has disappeared Minimal period of bed rest for children is three months Only rarely will the patient need to stay in bed longer than a year In adults with rheumatic fever for the first time and no evidence of cardiac involvement heart damage is unlikely It is therefore safe to be more lenient with regard to bed rest In some persons the sedimentation rate levels off just above normal and continues at this plane for many months For such patients it is usually not practicable to continue bed rest until the rate becomes normal Transition from bed rest to physical activity should be gradual

Proper diet sometimes contributes toward improvement Anemia usually does not improve until the active rheumatic process subsides

Salicylates have a striking effect on fever joint manifestations pains elsewhere in the body and often on pericardial effusion and leukocytosis but do not lower the sedimentation rate The usual dose of sodium salicylate or acetylsalicylic acid is ½ ¾ gr per lb body weight every 24 hours divided into four or six doses If necessary salicylates can be given rectally and rectal irritation can be avoided by incorporating the drug in corn starch solution Occasional patients have allergic reactions to salicylates Sodium bicarbonate given simultaneously with acetylsalicylic acid may prevent gastric irritation from the latter but if heart failure is present it may be better to use enteric coated preparations If salicylates cause tinnitus and deafness therapy should be temporarily discontinued In an occasional patient salicylates reduce plasma prothrombin concentration and if bleeding occurs it is wise to give about 1 mg synthetic vitamin K/Gm salicylates Hyperpnea may result from the stimulating effect of the salicylate molecule on the respiratory center and in an occasional patient occurs with small doses

Antibiotics do not effect the course of acute rheumatic fever and sulfonamides seem actually harmful during

evidence of heart disease at the termination of the first attack Of the 219 76 7 per cent showed no evidence of heart disease 10 years later Only 5 per cent of this group classified as having potential heart disease had died of rheumatic infection or bacterial endocarditis in the 10 year period

Of the 318 persons with rheumatic heart disease at onset only 30 showed disappearance of signs of cardiac involvement during the subsequent 10 years Of this group with rheumatic heart disease at onset 42 1 per cent had died of rheumatic infection or bacterial endocarditis in the 10 year period during which they were under study

The most significant prognostic factor so far as the initial illness was concerned was related to presence or absence of obvious signs of cardiac damage Chorea at onset was relatively benign in patients with heart disease This observation confirms the previously well known fact that chorea is less frequent in patients with carditis than is polyarthritis or other types of rheumatic infection

Ten years after onset 60 3 per cent of these rheumatic persons were leading normal existences with little or no limitation of activity Most persons without functional incapacities had no clinical evidence of heart disease at termination of the initial attack Rheumatic infection was the cause of death of 24 4 per cent of the total group most of the deaths occurring among the patients whose rheumatic heart disease accompanied the original attack Death occurred in only 5 per cent of the group with an original diagnosis of potential heart disease as compared with a death rate of 42 per cent among those diagnosed as having rheumatic heart disease at onset

Management of Rheumatic Fever and Rheumatic Heart Disease Benedict F Massell[5] (House of Good Samaritan Boston) believes it advisable to keep patients with active rheumatic fever in bed until all clinical and laboratory evidence of infection has subsided Tem

(5) M esota Med. 31 633 646 J n 1948

twice weekly the first two weeks once a week for the next two weeks and thereafter every two weeks until three months have elapsed At each visit urine should be tested for albumin and sediment and the blood for hemoglobin and leukocyte levels Differential blood count need be done only if the total white count is less than 5 000 It is advisable to administer sulfonamides throughout the year

Penicillin is not toxic but is as yet too expensive for continued use in rheumatic fever prophylaxis During acute respiratory infections it should be administered in 25 000 unit doses every three hours intramuscularly or in 300 000 unit doses in beeswax and oil intramuscularly once daily As soon as the temperature is normal 100 000 200 000 units of penicillin may be given orally three or four times a day

Though moderate climate will not influence the course of an acute attack of rheumatic fever it may help prevent recurrences

Antibiotics should be given to patients with acute rheumatic fever whenever they have severe respiratory infections operations or tooth extractions

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HYPERTENSION

Despite the advances of the past decade the pathogenesis of hypertension remains obscure The strong evidence that hereditary and endocrine factors are important in many instances is illustrated by the first three articles which follow

Aside from those rare conditions (such as adrenal medullary tumor and coarctation of the aorta) in which the cause of hypertension may be removed treatment of essential hypertension (i e hypertension of unknown cause) may be considered as falling within three categories (1) Regulation of life (diet habits physical activity and emotional problems) plus symptomatic management This is the oldest and still the preferred therapeutic plan for most patients (2) Dietary management The value and limitation of the low sodium and the rice diets are considered in a number of the following articles The final story is yet to be completed but certain points seem clear (*a*) these dietary regimens are of limited or no value for most patients (*b*) they are of great value for certain patients (*c*) there is no magic virtue in rice The

the acute process Penicillin however can be given with out fear of its being harmful if other conditions exist which indicate its use

Heart failure in the course of acute rheumatic fever requires strict bed rest use of a diet containing no more than 2 Gm salt daily and diuretics Fluids may be given in as large quantities as the patient desires Massell recommends use of powdered ammonium chloride shaken sparingly from a pepper shaker or use of spices or salt free condiments to improve the taste of food during the low salt diet

Theobromine diuretics are recommended for patients in whom edema is not great Of the preparations avail able Massell finds theocalcin® a nontoxic substance the most satisfactory Most theobromine preparations are obtainable in 0 5 Gm tablets and the daily dose varies from 1 5 to 4 Gm daily depending on the patient s size When necessary mercurial diuretics with ammonium chloride are given in the usual manner

Digitalis is recommended in heart failure only for con trol of auricular fibrillation When rhythm is regular digitalis has little effect on the congestive failure of acute rheumatic fever and has the disadvantage of being ex tremely toxic

During the first year after recovery from an attack of rheumatic fever the patient should avoid all forms of vigorous physical activity Activity should be gradually increased thereafter the best measures being the pa tient s actual tolerance and the size of his heart The most important aspect of aftercare is prevention of re currence Exposure to persons with colds should be avoided particularly during the first six months or a year after recovery and during this period the patient should not go to regular school church movies or other crowded places Respiratory infections can be prevented by administration of sulfamerazine or sulfadiazine in daily doses of 0 5 to 1 Gm To detect sulfonamide tox icity which may result in renal irritation agranulocy tosis anemia rash or fever the patient s be seen

of 269 patients with essential hypertension 46 5 per cent of 96 with chronic nephritis and 44 4 per cent of 30 with acute nephritis

It seems that the number of probable or doubtful hereditary factors contributing to illness is much greater in hypertensives and tho e with chronic nephritis than in the over all hospital population The percentage rises when more family members have diseases indicative of hypertensive effects and is highest when both parents are affected It also seems clear that the same hypertensive heredity factors operate in both essential hypertension and chronic nephritic hypertension Despite diversity of the morphologic and clinical courses of the various types of hypertension Mayer and Rouillard believe that there is a common ground for all patients with hypertension this almost certainly is the kidney arterioles Whether they are affected by intrinsically renal or neurohumoral factor determines the type of hypertensive process but the hereditary factor probably represents a disturbance in control of the arterioles

Pathogenic Patterns of Essential Hypertension W Raab[7] (Univ of Vermont) reviews evidence pertaining to neurogenic causes of hypertension Cerebral hypoxia has been shown to cause hypertension in animals by increasing irritability of vasoconstrictor centers Such blood pressure elevations are thought to be mediated by the sympathetic system and vasopressor substances have been found in blood of these animals Hypertension has also been produced by prolonged intense sensory impulses

Acute blood pressure elevation has been produced by injection of epinephrine or posterior pituitary substances and prolonged hypertension by administration of various steroids especially desoxycorticosterone There are indications that epinephrine stimulates adrenal cortex secretions and that these secretions in turn sensitize arterial walls to vasoconstrictor effects of sympathomimetic amines

(7) E p M d. & S g 6 464 486 No embe 1948

rice diet has the combined advantages (and disadvantages) of being low in sodium protein cholesterol allergenic substances and (often) in total calories (3) Reduction of the sympathetic vasoconstrictor function This can be accomplished either by operation or by u e of sympatholytic drugs A number of years must pass before the comparative value of these two procedures in relation to each other and in relation to dietary management can be asses ed At present it appears wise to consider sympathectomy for those patients with hypertension who are under age 50 who lack evidence of serious renal impairment who are becoming progressively worse and who fail to respond to dietary management —Ed

Parallel Heredity of Essential Hypertension and Hypertension of Chronic Nephritis (Glomerulonephritis, Chronic Ascending Nephritis, Malignant Nephrosclerosis) G Mayer and J M Rouillard[6] (Strasbourg) have been struck by frequency of hypertension or its manifestations in antecedent and collateral family members of patients with renal hypertension They have tried to determine if the same heredity factors are not concerned in both essential hypertension and hypertension of chronic nephritis In the latter disease there are high diastolic pressure perimacular exudation and papillary edema of nephritic retinitis There is almost always renal symptomatology and malignant hypertension may result Autopsy reveals glomerulonephritis chronic ascending nephritis or malignant nephrosclerosis Questionnaires were filled out on hereditary factors by 1 875 hospital patients Presence of hypertension arteriosclerosis cerebral apoplexy paralyses uremia hematuria albuminuria and nephritis were considered indicative of probable hypertensive heredity Of doubtful hereditary importance were considered cardiac disease apoplexy (without description) and edema The authors agree that family histories are not too reliable or accurate but feel that variations from group to group should cancel one another In the entire hospital population 23 4 per cent had probable or doubtful hereditary indications of hypertension in the family of 1 526 patients who themselves did not have hypertension only 18 6 per cent had such probable or doubtful histories The incidence rose to 49 1 per cent

(6) Arch d mal du coeu 41 403-409 Septembe

of the antidiuretic posterior lobe hormones and the beneficial results of roentgen irradiation of the pituitary and or adrenal cortex Overdosage with desoxycorticosterone acetate elicits hypertension and hyperplasia of the adrenal cortex is common in persons with essential hypertension Adrenal cortex activity in countless alarm reactions during a lifetime may give rise to hypertension by causing vasoconstriction of the brain centers controlling vasoconstriction or of the kidneys which may then elicit either the renin angiotonin or the hydroxytyramine sympathin epinephrine mechanism or both

Adrenal Medullary Tumor (Pheochromocytoma) is described by Francis N Hatch Victor Richards and Ralph J Spiegl[8] (Stanford Univ) Pheochromocytomas are tumors of the adrenal medulla developmentally related to the sympathetic ganglions They are usually small and unilateral but may be as large as 5 in in diameter and in 10 per cent of patients are bilateral If malignant metastasis frequently occurs in the regional and thoracic lymph nodes liver and skeleton

Pheochromocytomas are most commonly seen during th third to fifth decades and cause recurrent paroxysms of generalized vasoconstriction with transient hypertension Hypertension may be persistent and in addition there may be symptoms of adrenal cortical insufficiency from pressure On the other hand there may be no symptoms Hirsutism and precocious genital development suggesting hyperfunction of the adrenal cortex have also been reported Histories as long a 16 years are recorded attacks may occur only at long intervals or as often as several times daily Palpitation is usually the first symptom but vague uneasiness lassitude weakness or local pain in abdomen chest or head may occur Vasoconstriction may produce cramps or colic in abdomen chest or head During a severe episode the patient is unmistakably ill and the attack may terminate in shock Pallor of the face and extremities is

(8) Am J M d 6 633 64 M y 1949

Chronic hypertension has also been produced by partial obstruction of one kidney Extracts of such kidneys exert vasopressor effects Renal hypertension has been produced by causing vascular sclerosis of kidneys by injection of desoxycorticosterone acetate Another renal mechanism thought to contribute to vasoconstriction is action of dopa decarboxylase an enzyme in the kidney which transforms dopa (the amino acid dihydroxyphenylalanine) into hydroxytyramine a mother substance of the sympathomimetic vasopressor amines sympathin and epinephrine Renal ischemia favors accumulation of hydroxytyramine Ischemic kidneys also produce a substance which sensitizes vascular walls to epinephrine

Several abnormalities indicate that central vasomotor reflex responsiveness is abnormal in essential hypertension Experiments indicating that this is true include carbon dioxide inhalation and breath holding holding the hand in ice water physical exercise pain and inhalation of ammonia all of which increase vasopressor effects in hypertensives Carbon dioxide loss by hyperventilation spinal anesthesia barbiturates and carotid sinus pressure produce greater vasodepressor effects in hypertension The neurogenic origin of hypertension in its prerenal stage is indicated by the effects of sympathectomy tetraethylammonium which blocks vegetative nervous system ganglions and sympatholytic drugs such as dihydroergotamine Chronic hypertension has been produced in animals by induction of cerebral ischemia It seems likely that cerebral ischemia from brain stem arterial disease in man might produce hypertension Hypertension as a sequel of cerebral concussion and encephalitis may have the same origin

Function of the anterior lobe of the pituitary directly or by way of the adrenal cortex in essential hypertension is suggested by the finding of hypertension in Cushing s and the adrenogenital syndromes and the finding of hypotension in Simmonds and Addison s diseases Further evidence is the finding of increased urinary excretion of anterior lobe hormones incr e l production

ated on for the adrenal tumor 3 died Patients who re covered have had complete relief

CASE 1—Woman 23 was subjected to splanchnic section for hypertension but during operation adrenal glands were not explored A month after operation she died of cerebral hemorrhage and pheochromocytomas were found at autopsy

CASE 2—Woman 32 with marked hypertension and an elevation of the basal metabolic rate was given subtotal thyroidectomy but continued to have a basal metabolic rate of + 40 At splanchnicectomy both adrenal glands were found enlarged The entire left adrenal and three fourths of the right adrenal were removed histologic section showed a typical pheochromocytoma in the left Adrenal cortical extract was given in large doses during the first nine postoperative days The patient recovered and more than two years later was in good health

CASE 3—Physician 26 was hospitalized for confirmation of his own diagnosis of pheochromocytoma For two years he had had episodes of tenseness nervousness tachycardia and palpitation during these attacks blood pressure was definitely elevated He declined a histamine test but operation was performed and a pheochromocytoma of the right adrenal gland was found and removed Two years after the operation he was well and had had no more attacks

Arterial Hypertension in the Chicken Previous workers had observed that cardiovascular and renal changes could be produced in chickens by adding sodium chloride to the drinking water These changes suggested the possibility that hypertension had developed in these animals Therefore R Lenel L N Katz and S Rodbard[9] (Michael Reese Hosp Chicago) measured blood pressures of chickens at frequent intervals before during and after periods of substitution of 0 9 and 1 2 per cent saline solution for drinking water

Average systolic and diastolic blood pressures increased progressively during the period of salt administration from an average of 132/117 mm Hg at the beginning of the increased salt intake to a maximum average value of 183/154 mm Blood pressure fell promptly to control levels after withdrawal of sodium chloride Similar observations were made during two periods of salt

(9) Am J Phy 1 152 557 56 M h 1948

common or there may be alternate flushing and blanch ing Tachycardia bradycardia and irregularities of cardiac rhythm may occur There is of course accentua tion of the aortic second sound accompanying rises in blood pressure which may be in the magnitude of 100 200 mm Hg systolic above the normal level Hypergly cemia and glycosuria may occur during attacks In about one third of the patients the tumor is palpable in the abdomen or flank and massage of these tumors has in duced attacks Attacks last from a few minutes to hours or days In at least half the patients crises occur spon taneously but in many instances attacks are precipitated by postural changes nervousness exertion pain consti pation or menstruation

Intravenous injection of 0 025 or 0 05 mg histamine base will cause a systolic pressure rise of at least 100 mm Hg in the presence of a pheochromocytoma This test has been positive in all patients described to date but is somewhat dangerous A preferable test utilizes ad renolytic action of benzodioxane first described in 1947 When this drug is used a continuous intravenous drip of normal saline is given to the unsedated patient and into this infusion 10 mg 933F (piperidyl methylbenzo dioxane) plus 30 mg 1164F ([2 4 dimethylpiperidyl] methylbenzodioxane)/sq m body surface is given for two minutes Duration of drug action is usually less than 15 minutes Blood pressure readings taken at frequent intervals before during and after injections into patients with pheochromocytomas were reported to fall a maxi mum of 50 75 mm Hg systolic and diastolic Side ac tions of benzodioxane are not serious

Pheochromocytomas must be treated surgically and it is recommended that duration of operation be kept at a minimum by use of two surgical teams to operate through bilateral paravertebral incisions made about 6-8 cm lateral to the spinal processes and centered just be low the twelfth rib Adrenal cortical insufficiency if pres ent should be controlled before during and after opera tion Among 24 patients with pheochr ma oper

ter not only because it is unpalatable but because it is difficult to maintain adequate restriction of sodium In addition relatively few patients blood pressures respond favorably Among some 50 patients treated by the authors with the low sodium diet under carefully controlled conditions in the hospital less than 20 per cent experienced reduction of blood pressure or other objective improvement Possibly more may respond if the diet is continued for years rather than months but as yet no one has studied such patients At present there is no method other than trial to determine which patients will respond to diet and which will not

Clinical Evaluation of Veratrum Viride in Treatment of Essential Hypertension was made by Edward D Freis and Joseph R Stanton (Boston Univ) They found veratrum a useful therapeutic agent in treatment of hypertensive crises severe long standing hypertension resistant to other forms of treatment and hypertension complicated by cardiac failure The authors recommend its use as an adjunct to diet therapy in routine management of hypertensive heart disease

Veratrum viride was administered orally as the whole powdered mixture of alkaloid to 40 patients with essential hypertension for periods up to 13 months The drug s hypotensive effects began to appear after 1 2 hours reached a maximum in 4 6 hours and largely disappeared in 14 hours To obtain maximal therapeutic benefit and to avoid toxic reactions of cumulative over dosage veratrum was administered at 12 hour intervals To provide even greater therapeutic safety the interval was further subdivided so that no more than 10 Craw units was ingested per hour Response to a given dosage varied greatly in different persons and gradual increase in dosage was necessary to avoid toxic side effects

Prolonged therapy in some patients resulted in diminution in cardiac size and reversal of electrocardiographic changes toward normal No toxic effects resulting in more than transient disability were attributable to the

( ) Am H t J 36 723 738 N mb 1948

administration and two periods of return to drinking of tap water Degree of hypertension appeared to depend on concentration of salt in ingested water Hyperplasia and *proliferation of glomerular tufts and Bowman s capsule* with capillary compression were found after long periods of substitution of saline for drinking water This hyper plasia was reversible

Production of hypertension in the chicken by high *salt intake appears pertinent to the general* problem of the genesis of hypertension The theory behind use of salt free diets in treatment of hypertension is given some support by these findings

Diet in Treatment of Hypertensive Disease is dis cussed by Irvine H Page A C Corcoran and Robert D Taylor[1] (Cleveland Clinic) Diets said to be useful in treatment of hypertension include (1) low calorie diet a successful form of treatment (2) low protein diet now largely abandoned but which should probably be re studied (3) low salt diet and the variation between the ordinary low salt diet and the drastic reduction (less than 200 mg sodium in urine) (4) Kempner rice diet and (5) low cholesterol diet With regard to diet and vascular disease in the average patient the condition of overweight indicates a low calorie diet azotemia and renal failure indicate a low protein diet and conditions such as sodium retention in congestive heart failure Cushing s disease and possibly hypertension indicate a low sodium diet The rice diet is low in sodium calories and protein and in a sense is a shotgun prescription However indications for sodium restriction are *better* met with a low sodium diet Diets low in sodium calories and protein decrease blood and interstitial fluid volume and this effect may be desirable in some patients How ever in a patient whose renal function is already preju diced *the low sodium* diet *may be dangerous* If the kid ney is unable to conserve sodium sodium depletion with renal failure and azotemia may occur

The low sodium diet is extremely difficult to adminis

(1) Postg d Med 5 11 218 M ch 1949

pertension in 12 dogs due to nephrosclerosis produced by repeated intravenous administration of streptococci has been found to respond to the Kempner rice diet One dog died and substantial reduction in blood pressure occurred in 10 of the other 11 All but one dog lost weight an average of 19 7 per cent of total body weight

Speculation has been rife as to the mechanism by which the Kempner rice diet reduces blood pressure Kempner himself claims that his patients maintain positive nitrogen balance despite the meager 20 Gm protein which the diet contains Careful observation by Schwartz of six normotensive subjects placed on the Kempner rice diet for eight days showed negative nitrogen balance in all Even after 90 days of rice diet nitrogen balance remained negative in the single hypertensive patient studied

Schwartz concludes that though the low salt intake of the rice diet requires further study the starvation particularly of protein produced by the diet plays a significant role in reduction of blood pressure Therapeutic effect of a bizarre regimen presented with enthusiasm is thought also to be important

Use of Rice Diet in Treatment of Hypertension in Nonhospitalized Patients Andrew W Contratto and Miriam B Rogers[5] (Boston) maintained 34 ambulatory hypertensive patients on the Kempner rice diet for six months Definite and persistent drop in blood pressure occurred in 24 In 16 systolic blood pressure dropped to 150 or below and diastolic to 100 or below

The rice diet is a practical inexpensive and simple method for reducing blood pressure but it requires understanding and co operation on the patient s part All patients lost weight during the first 10 or 20 days Determination of chloride excretion in 24 hour urine specimens used as a measure of the patient s co operation showed that most patients who adhered to the diet excreted less than 1 Gm salt in 24 hours after the first 2 weeks

(5) N w E gla d J M d 239 531 536 O t 7 1948

drug Side effects did however limit use of the drug in patients with only mild or moderate hypertension

Effect of Low Sodium Diet and Rice Diet on Arterial Blood Pressure Benjamin Rosenberg Alfred E Rosenthal and Milton B Rosenbluth[4] (New York Univ) studied nine patients with essential hypertension All were hospitalized throughout the study Blood pressures were taken twice daily during a control period of approximately one month immediately before dietary therapy was started During the control period diets contained approximately 2 100 calories and 6 Gm sodium chloride Subsequently effect of low sodium diet and/or rice diet was studied With few exceptions periods of observation on each of the two therapeutic diets lasted four weeks or more Low sodium diet was given to seven patients and four of these also received the rice diet One patient was given the rice diet alone and one who failed to adhere to diet was dropped from study Low sodium diet provided 1 800 calories 70 Gm protein and 300 mg sodium Rice diet contained 2 000 calories 20 Gm protein and 150 mg sodium

Of seven patients on the low sodium diet four experienced statistically significant diminution of blood pressure and three did not change Of five patients on the rice diet three showed statistically significant diminution of blood pressure but in only one was there a fall to normal values Effect of rice diet was only slightly greater than that of low sodium diet All patients experienced weight loss ranging from 4½ to 14 lb during periods of dietary restriction Despite fall in blood pressure in five patients there was no relief of symptoms Although the series of patients was admittedly small the authors believe that changes detected were not sufficient to warrant routine use of this therapy in management of essential hypertension

Rice Diet *Some Experimental Observations* are reviewed by William Schwartz[4] (Harvard Univ) His

(3) Am J Med 5 815 8 0 December 1948
(4) Bull N w E gl d M Cent 11 7 33 F bru y 1949

to four days Total amount administered varied between 8 and 32 cc

Significant fall in blood pressure occurred in five patients Of these four were followed up to six months In each instance blood pressure was maintained at reduced levels by adherence to the 200 mg sodium diet Appreciable blood pressure lowering was noted first on an average of 4½ days after the initial injection of mercuzanthin* An average of four injections was necessary to induce initial decline and an average of six injections was required to induce maximal decline

Plethysmograph studies on six patients showed pronounced increase in vasolability after sodium diuresis in five These changes were accompanied by increases in depressor response to tetraethylammonium chloride

In all but one patient retinal abnormalities regressed during sodium depletion This regression occurred even when blood pressure remained unchanged Headache was the chief complaint of six patients During treatment this symptom disappeared in five patients and was considerably alleviated in the sixth

Blood pressure previously lowered by the Kempner regimen became elevated when sodium was added to diet It is inferred therefore that the primary factor responsible for lowering blood pressure in the Kempner diet is sodium depletion

The authors believe that elevation of blood pressure in certain hypertensive patients results from mechanisms different from those which cause the vascular alterations demonstrated by plethysmograph and ophthalmologic study

Effect of Tetraethylammonium in Arterial Hypertension A Rune Frisk Sven Hammarstrom Henrik Lagerlof Lars Werko Gosta Bjorkenheim Alf Holmgren and Yngve Larsson[7] (Stockholm) injected tetraethylammonium (TEA) in doses of 5 mg/kg body weight into 71 patients with hypertension Before injection blood pressure and pulse rate were determined with

(7) Am J Med 5 807 814 D mbe 1948

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(7) Am J Med 5 807 814 D mb 1948

The diet contained 250 300 Gm rice (dry weight) daily Any kind of rice was used provided no sodium chloride or milk was added during processing All fruit juices and fruits were allowed except nuts dates avocado and any dried or canned fruit or fruit derivative to which substances other than white sugar had been added Usually no water was given and fluid intake was limited to 700 1 000 cc fruit juice daily Supplementary multiple vitamins were added

The diet was modified at approximately one month intervals In most instances blood pressure rose but slightly when the diet was liberalized in the following manner First addition consisted of one egg a week half a cup once a day of nonleguminous vegetable (carrots broccoli celery cabbage asparagus beets etc) boiled without salt and if desired a cup of coffee or tea once a day with sugar but without milk or cream no salt or fat was included in any modification The second modification consisted of addition of 4 oz lean meat fish liver or chicken three times a week an egg three times a week and a nonleguminous vegetable once a day In addition some patients were allowed two slices of salt free bread a day The third modification permitted 4 oz meat etc at one meal daily half a cup each of two nonleguminous vegetables one egg either boiled or poached three times weekly and a baked or boiled white or sweet potato twice weekly

Treatment of Hypertension by Accelerated Sodium Depletion is reported by Raymond S Megibow Herbert Pollack Gene H Stollerman Edward H Roston and John J Bookman[6] Regular ward diets were administered for two to three weeks to eight hypertensive patients and during this period numerous blood pressure determinations were made and other studies carried out A diet of 75 Gm protein 90 Gm fat 240 Gm carbohydrate and a maximum of 200 mg sodium was then given After five to seven days on this diet mercuzanthin* injections in doses of 2 cc were given at intervals of one

(6) J Mt S a Ho p 15 233 239 N D c 1948

sion present during its administration can be attributed to humoral mechanisms Effect of TEAC is exerted on autonomic ganglions

METHOD —TEAC 400 mg was injected intravenously Blood pressure recordings were made before injection and during maximal effects of TEAC i e the TEAC floor Fall in blood pressure produced by the drug was designated the TEAC response Blood pressure readings were made at minute intervals until there were three consistent readings before injection and at 30 60 second intervals for 6 10 minutes after injection or until pressure had begun to return to normal

After a control period patients were placed on diets containing 0 2 0 25 Gm sodium daily One patient with a low renal reserve was given 0 9 Gm To achieve even greater sodium depletion mercuhydrin® was administered to eight patients This regimen was continued for 7 21 days and TEAC tests were performed 2 19 times while the patient was on this regimen In six patients a further period of study was conducted on a diet containing 2 4 Gm sodium daily for 7 12 days In six patients several alternations of sodium balance i e several salted and desalted periods were possible A total of 268 TEAC tests were made

In five patients with benign essential hypertension there was greater fall in random blood pressure and/or TEAC floors during desalted than during salted periods Little lowering of blood chloride concentration was achieved by sodium restriction in these patients In seven patients with malignant hypertension and renal failure no significant changes occurred in random blood pressure TEAC floor or TEAC response despite significant lowering of blood concentration of sodium chloride in desalted periods

These experiments seem to demonstrate that in patients with benign essential hypertension and good kidney function the humoral component of peripheral resistance can be altered by changes in salt balance and that these alterations do not depend on lowering of blood chloride concentration The important change during sodium deprivation may be lessening of the humoral contribution to maintenance of increased peripheral resistance In patients with malignant hypertension and renal failure the humoral component of peripheral resistance

the patient recumbent until constant levels were obtained These determinations were repeated every minute after injection until blood pressure started to rise again in 10 20 minutes

The greatest diminution in blood pressure after TEA occurred in patients with highest original blood pressure Effect on pulse rate was about the same in patients with severe as in those with slight hypertension In patients whose original systolic blood pressures were below 200 mm and whose diastolic pressures were below 110 lowest blood pressure obtained after TEA was approximately the same as that achieved with bed rest alone In patients with higher blood pressures TEA caused blood pressure to fall below the lowest values achieved spontaneously

Fall in blood pressure and pulse pressure was greatest in oldest patients Analysis revealed that this phenomenon was not entirely the result of the fact that the oldest patients often had the highest blood pressures Greatest increase in pulse rate after TEA occurred in the youngest patients

Doses of 10 mg TEA/1 g were given to 19 patients who had previously been given 5 mg doses In some of these blood pressure fell further with the larger dose

Cardiac catheterization studies of three patients revealed that after administration of TEA fall in blood pressure in the pulmonic circulation was relatively greater than in the systemic circulation probably because of shift of blood volume toward peripheral blood vessels

Effect of Sodium Chloride Depletion on Blood Pressure and Tetraethylammonium Chloride Response in Hypertension William W Stead Morton R Reiser Samuel Rapoport and Eugene B Ferris[8] (Univ of Cincinnati) gave tetraethylammonium chloride (TEAC) to 12 hypertensive patients to elucidate the effect of sodium restriction Since this drug blocks transmission of nerve impulses any effects of sodium restriction on hyperten

(8) J Cl I t gat 7 66 777 \ emb 1948

that almost two thirds of the patients with hemorrhages in the eyegrounds failed to benefit from operation For these patients in particular it was decided to extend sympathectomy from the twelfth thoracic to the third or fourth thoracic ganglion

Records of 173 patients subjected to this more extensive operation six months to three years previously were reviewed Results were good (fall of 50 mm systolic and 20 mm diastolic with final blood pressure below 200/120) in 55 5 per cent of patients whose preoperative blood pressure dropped to normal on rest and who had no eyeground changes except increased light reflex (group 1) and patients whose preoperative blood pressure dropped to or near normal on sedation and who had arteriovenous nicking (group 2) They were good in 31 per cent of patients whose preoperative blood pressure dropped but little with sedation and who had hemorrhage or exudate in eyegrounds (group 3) and in 11 per cent of patients who e preoperative blood pressures did not drop on sedation and who had choked disks (group 4) Results were fair (systolic blood pressure drop of 30 mm and diastolic drop of 10 mm with final blood pressure above 150/100) in 16 8 per cent of patients in groups 1 and 2 24 5 per cent of those in group 3 and 22 2 per cent of those in group 4 (Figures refer to supine blood pressure readings) A good drop in orthostatic blood pressure was of course obtained much more frequently than was drop in supine pressure Of patients in groups 1 and 2 78 per cent reported marked relief of symptoms 63 per cent of those in group 3 and 33 per cent of those in group 4 reported relief

Certain criteria for sympathectomy in hypertension have been established at the Clinic Operation is rarel performed on patients with grade I fundi and with blood pressures that fall to normal on rest Such patients are observed for several years while psychotherapy is being used Patients over 50 are rarely operated on particularly if they are tolerating hypertension well Severe hemiplegia severe heart failure severe coronary insuffi

shows little tendency to be influenced by sodium depletion

Evaluation of Neurogenic and Humoral Factors in Blood Pressure Maintenance in Normal and Toxemic Pregnancy Using Tetraethylammonium Chloride Albert A Brust N S Assali and Eugene B Ferris[9] (Univ of Cincinnati) blocked sympathetic impulse transmission with tetraethylammonium chloride (TEAC) in 10 normal subjects 10 pregnant women at term and 23 women with toxemia of pregnancy TEAC studies were performed on all pregnant patients in both pre and post partum periods by injecting 400 mg TEAC intravenously and recording blood pressure at ½ minute intervals for 6 minutes and at 1 minute intervals for 10 30 minutes thereafter

TEAC blood pressure response and floor (lowest point to which pressure fell in the first five minutes after injection) deviated strikingly and consistently from normal in both toxemia of pregnancy and normal pregnancy at term In toxemias the floor was consistently elevated and fell to normal after recovery from toxemia In normal pregnancy the floor was consistently depressed and rose to normal after delivery Little fall in blood pressure followed administration of TEAC to normal nonpregnant women

Since TEAC blocks autonomic nerve impulses and eliminates neurogenic tone but does not lessen humoral tone the authors postulate that the hypertension of toxemia of pregnancy is supported by an excessive degree of humoral tone The striking depressor response to TEAC in normal term pregnancy suggests further that neurogenic mechanisms are more active in normal pregnancy than in toxemia

Results of High Dorsolumbar Sympathectomy for Hypertension are presented by James A Evans and Carl C Bartels[1] In 1942 a review of experience at Lahey Clinic with sympathectomy for hypertension showed

(9) J Cl n I t gat 27 717 7 6 N mbe 1948
(1) A I t Me l 30 307 3 9 F b u y 1949

that almost two thirds of the patients with hemorrhages in the eyegrounds failed to benefit from operation For these patients in particular it was decided to extend sympathectomy from the twelfth thoracic to the third or fourth thoracic ganglion

Records of 173 patients subjected to this more extensive operation six months to three years previously were reviewed Results were good (fall of 50 mm systolic and 20 mm diastolic with final blood pressure below 200/120) in 55 5 per cent of patients whose preoperative blood pressure dropped to normal on rest and who had no eyeground changes except increased light reflex (group 1) and patients whose preoperative blood pressure dropped to or near normal on sedation and who had arteriovenous nicking (group 2) They were good in 31 per cent of patients whose preoperative blood pressure dropped but little with sedation and who had hemorrhage or exudate in eyegrounds (group 3) and in 11 per cent of patients whose preoperative blood pressures did not drop on sedation and who had choked disks (group 4) Results were fair (systolic blood pressure drop of 30 mm and diastolic drop of 10 mm with final blood pressure above 150/100) in 16 8 per cent of patients in groups 1 and 2 24 5 per cent of those in group 3 and 22 2 per cent of those in group 4 (Figures refer to supine blood pressure readings) A good drop in orthostatic blood pressure was of course obtained much more frequently than was drop in supine pressure Of patients in groups 1 and 2 78 per cent reported marked relief of symptoms 63 per cent of those in group 3 and 33 per cent of those in group 4 reported relief

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ciency or previous myocardial infarction and poor renal function are contraindications An attempt is made to rule out the possibility of glomerular nephritis coarctation of the aorta polycystic kidneys pheochromocytoma brain tumor Cushing s disease systolic hypertension of arteriosclerosis and unilateral Goldblatt s kidney Operation is not done on patients with choked disks and fixed blood pressure Patients with only arteriovenous nicking and labile blood pressures are operated on particularly if there is evidence of advancing degenerative cardiovascular or renal disease Good results may be expected in 73 per cent of such patients Many patients with hemorrhages exudates or choked disks are operated on if they have a fair degree of lability of blood pressure and none of the contraindications stated Families of such patients are told that without operation four year survival rate is 20 per cent and with operation it may be 50 per cent Chronic pyelonephritis is not considered a contraindication to operation if nonprotein nitrogen is not elevated and intravenous pyelograms still show fair concentration

Although the present series of patients has been followed for a shorter time than those treated with lower sympathetic resection high dorsolumbar sympathectomy from the fourth thoracic to the second or third lumbar ganglions appears approximately to double good results in patients of groups 1 2 and 3 The authors are loathe to consider this type of operation with its prolonged uncomfortable convalescence as a prophylactic operation for benign hypertension but urge it on patients under 50 with spastic exudative and hemorrhagic retinal arteriolar changes moderate cardiac damage signs of early nephrosclerosis and labile blood pressure

Surgical Treatment of Hypertensive Heart Disease and Heart Failure of Hypertension. In surgical treatment of arterial hypertension by sympathetic denervation hypertensive heart disease and especially heart failure have been considered formal contraindications to opera

tive procedure Ignacio Chavez and Luis Mendez[2] (Inst of Cardiolo_gy Mexico D F) point out that unfortunately patients with these handicaps are precisely the ones who most urgently need lowering of blood pressure

Because in their opinion the many tests proposed so far for measuring and eliminating the neurogenic factor as the main cause of sustained vascular spasm cannot be relied on they recommend operation to patients who need it if there is no positive contraindication Patients classified hypertensive with secondary heart disease have been generally considered undesirable for surgery Arteriosclerosis and structural visceral involvement in these patients have been regarded as irreversible and contraindications for operation The authors believe this conception is mistaken Possibly brain and kidney damage is unlikely to regress but this is not true of the heart In cardiac damage the most frequent complication the physician may feel justified in insisting on operation and the patient who is confronted with an already existing ominous risk may well accept the lesser risk of surgical treatment It is true that anatomic damage has already occurred in the heart however since medical treatment cannot suppress the cause of the damage surgery is the only means for helping the strained heart Patients with elevated blood pressure and with definite cardiac change should be operated on before they develop functional cardiac insufficiency

In dealing with patients with more advanced hypertensive disease and severe visceral complications—heart failure renal insufficiency and severe encephalopathy—it has long been agreed that surgery should not be performed However the authors suggest that such a positive decision should be modified even for this group It is conceivable that the mechanical factor of overwork and strain plays a decisive role in producing and later maintaining heart failure The authors operated on 11 hypertensive cardiac patients all of whom were in heart

(2) Am H t J 37 5 3 530 Ap 1 1949

failure in some it was of extreme degree One died of cerebral hemorrhage 11 days after operation another died the day after operation of occlusion of the aqueduct of Sylvius the result of an overlooked old meningitis and a third patient died of uremia 10 months after surgery The other eight patients were cured of heart failure and have not relapsed during follow up periods ranging from one to three years Almost every patient has resumed a normal life and blood pressure if not normal is only slightly elevated

In the authors opinion instead of a contraindication hypertensive heart disease is fundamentally a formal indication for surgical treatment as the only means of staying myocardial damage Heart failure when not accompanied by advanced lesions may sometimes be corrected by operation even in protracted cases in which digitalis has failed

Hazards of Thiocyanate Therapy in Hypertension Donald L Kessler and Laurence E Hines[3] (Chicago) report three illustrative cases

Case 1—Woman 48 was hospitalized because of confusion disorientation and hesitant speech Blood pressure was 260/114 For three months she had been given thiocyanates serum thiocyanate level being maintained between 8 and 15 mg per cent Although thiocyanates were discontinued on admission serum thiocyanate level 10 days later was 8 mg per cent After 18 hospital days mental confusion subsided despite continued elevation of blood pressure On discharge serum thiocyanate level was 5 5 mg per cent

Case 2—Woman 64 was hospitalized because of weakness palpitations slurred speech inability to concentrate disorientation and soreness of the mouth tongue and lips Blood pressure was 190/85 She had been given 0 3 Gm potassium thiocyanate three times daily for a month Two weeks before hospitalization thiocyanate level was 8 mg per cent On admission thiocyanate therapy was discontinued and eight days later serum thiocyanate concentration was 10 mg per cent At this time she was asymptomatic After two weeks hospitalization she was discharged with serum thiocyanate level of 8 mg per cent

Case 3—Man 52 was hospitalized because of stupor pro

(3) J A M A 139 549 551 Oct 23 1948

fuse salivation and sweating and auditory and visual hallucinations In addition he had a generalized exfoliative dermatitis The thyroid was diffusely enlarged and blood pressure was 130/90 Because of partial paralysis of the left side and blood pressure of 260/150 thiocyanate 0 26 Gm had been administered three times daily for three weeks before hospitalization During this time blood pressure dropped but the symptoms described developed

On admission red cell count was 3 900 000/cu mm hemoglobin value 12 Gm per cent icterus index 60 units nonprotein nitrogen value 60 mg and thiocyanate level 25 3 mg per cent Pneumonia developed and he died the seventh hospital day

Autopsy showed generalized icterus exfoliative dermatitis extensive liver necrosis arteriolar nephrosclerosis cerebral edema and softening of the internal capsule

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DISEASES OF CORONARY ARTERIES

The articles selected illu t ate that p ogress is being mad in three d rections (1) use of vasodilator drugs (2) reduction of the demands on the heart and (3) attempts to increase blood supply to the heart At present it appears that the best method of management of coronary artery disease consists of avoiding the conditions wh ch precipitate the pain weight reduction in obese patients restriction of cholesterol in the diet and free use of nitroglycerin not only when pain is present and when it is likely to occur but also routin ly three to four times daily in order to maintain coronary d latation and to favor the development of collateral channels —Ed

Coronary Artery Disease in Men 18 39 Years of Age Report of 866 Cases, 450 with Necropsy Examination Wallace M Yater Aaron H Traum Wilson G Brown Richard P Fitzgerald Murray A Geisler and Blanche B Wilcox[4] found little that differentiated myocardial infarction clinically or pathologically in men under 40 from that occurring in men of older age groups A family history of cardiovascular disease was four times as common among patients who survived myocardial infarction than in a control group On induction into the Army weight of men with coronary artery disease corresponded to average weight of all inductees and during their army careers they gained weight almost in the same relative degree as other soldiers

(4) Am H t J 36 683 7 N mb 1948

Only 24 men were considered clinically to be truly hypertensive but 27 9 per cent had systolic blood pressures above 139 mm Hg and 19 1 per cent had diastolic pressures above 89 mm Time of year and geographic location had no apparent influence in precipitating death Onset of terminal illness or coronary attack occurred relatively more often during strenuous activity The proportion of attacks occurring during strenuous activity was more than twice as great as the proportion of time spent in such activity and the proportion of men stricken while asleep was about one third that of the proportion of time normally spent in sleep

About half the men had had cardiac symptoms before onset of the attack Symptoms were chiefly isolated attacks of coronary insufficiency with pain weakness sweating and sometimes dyspnea Of the 450 patients who died 83 3 per cent died within 24 hours of onset

Pain was present in 98 4 per cent and was the primary or first symptom of most of these patients Shock was the next most common symptom and occurred in 17 per cent Incidence of shock was almost eight times as high among the men who died as among those who survived Dyspnea nausea and vomiting nervous manifestations including unconsciousness and convulsions indigestion and diarrhea frequently occurred

Radiation of pain was recorded in 67 per cent of cases Chest pain was accentuated by deep inspiration in 10 per cent of survivors despite the fact that none of these men had detectable pericardial or pleural effusion

Of 54 men who died during hospitalization congestive failure developed in 13 embolization in 5 and convulsions in 6 Of 400 survivors 16 were thought to have cardiac enlargement Poor heart sounds were noted in 72 premature ventricular contractions in 57 paroxysmal auricular tachycardia in 2 auricular fibrillation in 2 and auricular flutter in 1 In all instances arrhythmias were transient Systolic murmurs were heard in 33 men and diastolic murmurs in 2

In 20 per cent of men blood pressure and in 14

per cent it fell durin, the attack In 70 per cent blood pressure remained normal or returned to normal within 24 hours after the initial period of hospitalization and continued normal thereafter In 22 per cent of patients whose pressure either rose or fell during the attack the level became normal 48 hours or more after onset

Electrocardiography indicated that there was anterior infarction in 176 posterior infarction in 113 and lateral infarction in 56 No localizing changes were found in 55 Temperature white cell count and sedimentation rate were elevated in 58 per cent two of these three abnormalities were present in 28 per cent and one abnormality occurred in 12 per cent In only 2 per cent were temperature white cell count and sedimentation rate all normal

Recovery was asymptomatic in 57 per cent There was recurrence of pain in 25 per cent congestive failure in 2 per cent pulmonary congestion in 4 per cent dyspnea without rales in 5 per cent pulmonary infarction in over 1 per cent and pleural effusion in almost 1 per cent Another attack of acute myocardial infarction occurred in 17 per cent of the 400 who survived and in 28 of the 400 congestive failure later developed Of the 361 survivors with adequate follow up studies 50 per cent returned to full time employment and 41 per cent have not been able to work at all

Examinination of the heart at autopsy revealed little to differentiate the condition from that in older patients dying of myocardial infarction

Pain Syndromes of Chest Muscles Resemblance to Effort Angina and Myocardial Infarction and Relief by Local Block Janet Travell and Seymour H Rinzler (Cornell Univ) point out that closure of the coronary arteries results in reflex spasm of the chest and arm muscles just as acute appendicitis or any form of the acute surgical abdomen result in reflex rigidity of the abdominal musculature Such abnormal impulse from the heart may lead to development of a self perpetuating reflex which may be maintained for long periods by

(5) Canad M A J 59 333 338 Octob 1948

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Whatever the origin of pain the authors believe that it should be relieved. Pain itself may reflexly diminish the caliber of coronary vessels and so contribute to further damage to the myocardium. In addition when pain is not suppressed the excessive restriction of activity which may result often leads to physical and mental deterioration. Local block therapy by procaine infiltration or ethyl chloride spray is indicated for relief of chest pain whether the somatic manifestations are believed to be skeletal or visceral in origin. Relief of pain by these measures does not prove that the cause of pain is primarily somatic since under suitable conditions cardiac pain may likewise respond to local block of appropriate somatic structures.

Management of Acute Coronary Thrombosis and Its Complications Samuel A. Levine[6] (Harvard Univ.) believes that most patients with coronary thrombosis recover or die without regard for what the physician does. For occasional patients however treatment may be life saving.

A life may be saved in the presence of sudden collapse *by subcutaneous injection of adrenalin.* Though it has been the practice to keep patients with coronary occlusions *in bed for six weeks and away from work for* three to six months many can be allowed out of bed in *three weeks and most should go back to work* at least part time much sooner than they have heretofore been permitted. *It is not always desirable for the patient to be* flat in bed during the first weeks after myocardial infarction. The patient who is short of breath is probably better off sitting in a chair with feet hanging down so that blood pools in the lower extremities rather than in the lungs where it causes suffocation.

It is suggested that the patient is the best judge of the necessity of oxygen. During the first few days he often feels better with oxygen and if so it should be used. It is difficult to be sure whether pain is affected by oxygen.

Though Levine fears any intravenous medication after

(6) Con t cut M J 1 985 989 N mb 1948

skeletal muscles In effect a secondary pain syndrome based on spasm of somatic musculature may be created by impairment of coronary circulation

Other patients may have chest or arm pain with no evidence of organic heart disease Diagnosis may remain uncertain because the purely somatic pain syndrome resulting from fatigue and strain of voluntary muscles is overlooked Under such circumstances the patient s activity is likely to be greatly limited Among the factors which may contribute toward perpetuation of the somatic pain cycle are prohibition of exercise and lack of normal use of voluntary muscles

In differentiating somatic muscular pain from cardiac pain the authors find many difficulties In their experience it is not true that substernal pain on effort is necessarily due to coronary artery disease and precordial pain may originate from somatic or other cardiac causes They have reproduced cardiac pain in every detail by stimulation of trigger areas of chest muscles T wave changes may result simply from pain of striated muscle Nitrites in an occasional patient even relieve skeletal muscle pain Though accentuation of pain on movement of trunk or arms suggests the somatic origin of the pain this is not the only criterion because trigger areas may be so located that they do not produce any demonstrable restriction of motion

Some criteria are reliable however Signs of tissue necrosis and circulatory collapse suggest strongly that the pain is originating in the cardiac muscle Absence of trigger areas rules out skeletal muscle as the cause of pain unless trigger areas are located in the retrosternal striated muscle of the chest wall where they are not accessible to palpation A primarily somatic origin of chest pain is suggested by a rheumatic tendency in a patient or finding that painful motion elsewhere in the body is attributable to trigger areas in appropriate muscles If the distance which the patient can walk without pain fluctuates widely a large somatic component in the etiology of the pain is likely

wild in Eastern Mediterranean countries Decoctions of its seeds have been used by the local population as an antispasmodic since ancient times Chance observation of a patient whose angina had definitely improved during treatment with tincture of Ammi visnaga in the hope of passing a renal calculus aroused the authors interest in the drug Comparative experimental observations on the actions of khellin and aminophylline on coronary circulation and smooth muscle on dog heart lung preparations indicated that khellin is at least four times more effective as a coronary dilator

Khellin was given to 250 patients with angina of effort or decubitus and 50 patients with coronary thrombosis with or without angina during recumbency It was used

RESPONSE TO KHELLIN OF 250 PATIENTS WITH ANGINA PECTORIS

Grade of Angina Pectoris	Response to Treatment		
	Good	Moderate	Negative
Mild	68	12	—
Moderate	56	55	4
Severe	16	18	21
Total	140	85	25
Percentage	56	34	10

either in continuous treatment to prevent or diminish number of attacks or occasionally for relief from actual attacks To eliminate possible interference of a psychic element placebos were administered at times or the dose of khellin was suddenly reduced Khellin was administered orally to most patients 1 or 2 cc of a liquid extract containing 50 mg/cc of the active principle or as tablets each containing 50 mg Intramuscular injections of 2 cc once or twice daily were used during anginal attacks

Response to khellin was considered good when anginal attacks ceased or became infrequent and mild moderate when they diminished in frequency and severity and negative when no favorable change occurred Results are summarized in the accompanying table In many patients clinical improvement was confirmed by electrocardiograms

a coronary occlusion he believes that dehydration should be avoided by intravenous use of 5 per cent glucose if there is no pulmonary edema

Chest x rays after acute coronary thrombosis almost invariably reveal pulmonary congestion This congestion is often found before moisture can be heard with a stethoscope Breathlessness is the first indication During pulmonary congestion intravenous administration of fluids should be avoided and in rare instances phlebotomy may be a great help

Whether or not plasma should be administered in shock depends on the presence of pulmonary congestion If the patient is in severe shock and still can lie flat without dyspnea for an hour or two plasma should be considered

When Adams Stokes attacks occur after myocardial infarction Levine feels justified in administering adrenalin® 0 3 0 5 cc of 1 1 000 solution every 2 hours for 48 hours If tachycardia of the ventricle supervenes a test dose of 0 2-0 3 Gm quinidine is given orally and thereafter it no untoward results occur 0 4 0 6 Gm is given every few hours Quinidine can be administered intravenously if the situation is urgent It can be given in 100 200 cc of 5 per cent dextrose during the half an hour with an ink writing electrocardiograph recording during the injection so that quinidine can be stopped when tachycardia ceases Though it is usually less effective than quinidine 2-4 Gm magnesium sulfate intravenously occasionally stops ventricular tachycardia

The value of anticoagulants in treatment of myocardial infarction is not yet thoroughly established but the information accumulating may in the next few years establish them in routine use The value of digitalis after myocardial infarction is uncertain

Coronary Vasodilator Action of Khellin was investigated by G V Anrep M R Kenawy and G S Barsoum[7] (Fouad I Univ Hosp Cairo) Khellin is the active principle of Ammi visnaga a plant which grows

(7) Am Heart J 37 531 54 Ap 1 1949

erately Toxic reactions necessitated discontinuance of therapy in two patients and a third relapsed despite continuous treatment

Since evaluation of angina pectoris is usually a subjective matter the authors performed functional hypoxemia and exercise tolerance tests on all patients with angina before and at regular intervals during treatment Hypoxemia tests were done with 10 per cent oxygen and 90 per cent nitrogen until anginal pain occurred Electrocardiograms were taken before and every five minutes during the test when the patient noted pain and at the end of the test Pulse and blood pressure were recorded and oxygen saturation of blood was determined Krogh s bicycle ergometer with increasing loads was utilized for exercise tolerance tests During the test pulse and electrocardiographic tracings were registered Eight of the nine patients with angina showed marked and lasting *improvement during long-continued methylthiouracil* treatment and this improvement was recorded objectively during tests In most cases hypoxemia and exercise tests showed improvement

Usually it was necessary to continue treatment for three to six months before clinical improvement occurred and six to eight months before reduction of thyroid function was clinically evident When thyroxine storage in the thyroid gland was exhausted it was easy to maintain the basal metabolic rate at the desired low level with doses of 15 50 mg methylthiouracil daily

In most cases symptomatic response and lowering of basal metabolic rate occurred at the same time Five patients however showed marked clinical improvement without pronounced lowering of the metabolic rate In these patients there was a rise in serum cholesterol which was interpreted as indicating that methylthiouracil had blocked thyroxine synthesis

Experimental Study of Collateral Coronary Circulation Produced by Cardiopneumonopexy In view of the prevalence of coronary artery disease several intensive studies have been directed within the last decade toward

Among the 50 patients with recent coronary thrombosis treated with khellin the drug controlled and relieved anginal attacks which followed thrombosis during the period of bed rest as well as after recovery in 21 patients who had such attacks Mortality rate in the khellin treated group was similar to that in a control group

No habituation to the drug seemed to occur Even after it was used for two years it was still effective No toxic effects were encountered during its trial for such periods The drug has a prolonged action and remains in the circulation many hours

The authors conclude that khellin can be used successfully as a coronary dilator in treatment of deficient coronary circulation

Methylthiouracil in Treatment of Congestive Heart Failure and Angina Pectoris Results of Prolonged Treatment A Rune Frisk and Inga Lindgren[8] (Stockholm) report success from administration of methyl thiouracil to seven patients with congestive heart failure and nine with angina pectoris An initial dose of 400 500 mg daily divided into doses of 100 mg was administered during the several months the patients were in the hospital 100 mg was then given three times daily this dose being continued until basal metabolic rate was lowered or significant improvement had occurred At this time the dose was decreased to 100 or 200 mg daily and was then adjusted according to clinical improvement and basal metabolism In some cases daily doses of 15 50 mg were sufficient for maintenance A basal metabolic rate of about —15 was the goal None of the patients were thyrotoxic before treatment was instituted

All patients with congestive heart failure had mitral stenosis and all belonged to class IV or III before methylthiouracil treatment was instituted None had shown significant response to usual therapy with bed rest digitalis and mercurials On methylthiouracil four patients had considerable improvement which was maintained for long periods The other three improved mod

(8) A ta med. Sc d 13 (9 90 1949

superficial vessels in the myocardium microscopically but not grossly

For comparison with results of cardiopneumonopexy on the normal heart a second group of experiments was performed to determine the effect on the ischemic myocardium In 23 control dogs simple ligation of the anterior descending branch of the left coronary artery was done In a second group of 19 dogs ligation followed cardiopneumonopexy at an interval of 14 154 days Mortality among the 23 controls was 48 per cent whereas that among the 19 dogs prepared by cardiopneumonopexy before ligation was only 21 1 per cent These figures thus seem to indicate the beneficial effect of cardiopneumonopexy on survival after ligation of the anterior descending branch of the left coronary artery though they do not statistically establish this point Gross and microscopic comparison of specimens from these two groups of dogs revealed also that less extensive infarcts occurred in animals on which cardiopneumonopexy was performed before ligation of the coronary artery Severe infarctions occurred in 75 per cent of animals with simple ligation but in only 23 per cent of those with ligation after cardiopneumonopexy Injection of 10 per cent suspension of india ink in blood at normal pressures revealed considerably greater filling not only of superficial vessels but of deep ones after cardiopneumonopexy in hearts rendered ischemic by coronary artery ligation than in normal hearts after cardiopneumonopexy

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CONGESTIVE HEART FAILURE

The value of dietary restriction of sodium chloride and of mercurial diuretics in patients with congestive failure is well established However these procedures may be hazardous when carried to the point of sodium depletion The severer forms of sodium deficiency may be recognized by rapid rise in the nonprotein nitrogen level of the blood and call for replacement therapy

Lithium salts although a satisfactory substitute for sodium chloride so far as taste is concerned may be toxic especially when there

devising means of producing collateral coronary circulation Several possible sources of such a collateral blood supply exist the thoracic wall including the pectoral muscles internal mammary artery and intercostal arteries and the pericardium omentum and lung After consideration of the various methods reported B Noland Carter Edward A Gall and Charles L Wadsworth[9] (Univ of Cincinnati) decided that the lung appeared to provide the most effective source for a collateral blood supply to the heart They therefore attempted corroboration of previously reported successful results

TECHNIC—Thoracotomy incision was made in the left fourth interspace in dogs and after injection of 5 cc of 2 per cent procaine solution through a small opening in the pericardial sac this opening was prolonged superiorly to within 1 cm of the left auricular appendage and inferiorly to within 2 5 cm of the tip of the apex The anterior descending branch of the left coronary artery was identified and its midportion used as the center for a circular window 4 5 cm in diameter which was made in the parietal pericardium Three or four interrupted mattress sutures were placed between the medial edge of the window and the medial border of the middle lobe of the left lung Finely divided sterile asbestos powder mixed in sufficient saline solution to form a paste was applied to the surface of the exposed myocardium and the opposed under surface of the left middle lobe Mattress sutures were pulled up and tied the lung was inflated and the wound was closed There was no operative mortality except for that resulting from complications of infection

In 12 normal dogs prepared by cardiopneumonopexy the only significant difference between pre and post operative observations was development of typical electrocardiographic evidence of pericarditis in all dogs postoperatively Dogs were killed between 13 and 116 days after operation and heart and lungs were removed and injected to determine grossly and microscopically whether new vascular channels could be demonstrated between the normal myocardium and the adherent lung in dogs with no functional impairment of coronary blood supply Injections of 10 per cent suspension of india ink in blood at normal pressures revealed some filling of

(9) S gery 25 489 509 Ap 1 1949

mg as has been recommended is often hazardous and may produce toxic effects after some months use

Rapid Digitalization There is no unanimity on the best preparation to use for rapid digitalization nor on the best way to give the preparation of choice A comparison of series of patients on different drugs with a digitalis effect is available but the relative value of two or three preparations in the same patient has seldom been reported William Evans Peter Dick and Byron Evans (London Hosp) designed a clinical trial to discover the preparation most effective for rapid digitalization when given orally or intravenou ly by comparing the effect of as many preparations as possible in the same patient and under the same conditions Relative value of strophanthin ouabain and k strophanthosid digoxin digitoxin lanatoside C digitalis leaf and tincture of digitalis was studied in *20* patients with rapid auricular fibrillation and slight or moderate congestive heart failure Fall in ventricular rate in auricular fibrillation was considered the most satisfactory index of digitalization but improvement in objective si ns of failure and diuretic response were also observed

TECHNIC—After a few days preliminary ob ervation and after insuring that no digitalis had been given during the previous seven days the first preparation was given Apical rate was counted over three con ecutive half minutes and respiratory rate and blood pressure noted The drug was then given and heart rate counted for three consecutive half minute periods every quarter of an hour until it had ceas d to fall during 1/2 2 hours No further digitalis was then given for 3 14 days until ventricular rate had returned to its previous level and *effects of th previous preparation had worn off* Number of tests that could be done in each case was thus limited by failure of the ventricular rate to ri e to a comparable level after a variable number of tests Digitalis effect was classified as good when fall in heart rate within four hours was 75 per cent of the maximal fall produced by any preparation in that patient moderate between 50 and 75 per cent and slight below 50 per cent

Strophanthin 1/100 gr intravenously gave inconstant and poor results In a dose of 1/60 gr it produced a good

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[-] B + H t J 10 103 1 1 Ap 1 1948

is pre existing depletion of sodium Pending further knowledge lithium salts should not be used —Ed

Amount of Digitoxin (Digitaline® Nativelle) Required for Adequate Digitalization Harold J Stewart and Abbott A Newman[1] (Cornell Univ) have found 1 2 mg digitoxin insufficient to achieve adequate digitalization in most patients when given either intravenously or orally Average amount of digitoxin required for adequate digitalization of the authors patients was approximately 2 mg if given in 24 hours Among these patients there was no apparent difference in total dose required for adequate digitalization within 24 hours whether the drug was given in a single dose or divided doses

When adequate slowing of the heart was attained nausea and vomiting occurred more frequently with digitoxin than with whole digitalis leaf

Average maintenance dose of digitoxin was between 0 1 and 0 2 mg For most patients who were adequately digitalized 0 2 mg as a maintenance dose was too large It was more difficult to keep patients in equilibrium by maintenance doses of digitoxin than with the whole leaf

For digitalization with digitoxin orally the following schedule is recommended 0 8 mg followed in four hours by 0 5 mg by 0 3 mg after another four hours by 0 2 mg four hours later and then by 0 2 mg after another four hours if necessary Doses after the first are not to be given if ventricular rate slows to 75 or if nausea or vomiting occur

In hyperthyroidism with auricular fibrillation amounts of digitoxin required to slow ventricular rate are larger than when basal metabolic rate is normal

Though many claims have been made that 1 2 mg digitoxin constitutes a full digitalizing dose in the authors *opinion most* patients are *not fully* digitalized with this amount It appears safe in many instances to give 1 2 mg intravenously in a single dose simply because for most patients this does not constitute a digitalizing dose Furthermore a maintenance dose of 0 2

(1) Am Heart J 36 641 667 November 194

sodium chloride and of water diminished after gross hemorrhage into the gastrointestinal tract If large quantities of saline but no water are administered plasma chloride level is increased and large amounts of potassium are found in urine despite normal potassium concentration of serum

Increased serum chloride concentration with diminished urinary output of sodium and chloride is occasionally found in severe dehydration shock and edema from hypoalbuminemia or from cardiac failure with restricted fluid intake In these conditions cardiac output is diminished and increased excretion of water and electrolytes follows correction of cardiac output Urinary excretion of sodium chloride in patients with edema due to hypoalbuminemia increases when blood volume is raised by transfusion In patients with cirrhosis the same diuretic effect follows intravenous injection of the patient s own ascitic fluid

In previously healthy persons with acute heart failure retention of salt and water precedes development of backward failure At the time this occurs signs of forward failure are frequently subsiding

It is postulated that urinary excretion of water and salt diminishes when cardiac output diminishes This mechanism maintains volume of blood and extracellular fluid venous pressure and heart output within narrow limits in normal persons but in the presence of hemorrhage or shock plasma volume increases In the same manner volume of extracellular fluid and edema increase when blood volume is decreased by hypoalbuminemia venous return insufficient (as from cirrhosis) or cardiac function impaired as when cardiac output is subnormal in the presence of normal or high venous pressure In all of these situations retention of salt and water results not from disturbance in kidney function but from adaptation of the kidney to the circulatory requirement by hyperfunction of the kidney tubules

Patients with diminished cardiac output retain salt and water in equivalent amounts When the amount of

effect in three of four cases but this dose is much above what most authors consider the maximal safe dose Strophosid* gave better results than strophanthin it had a good effect in five out of nine cases and had a rapid action in three It worked better than strophanthin in two of three trials and as well as strophanthin in one But it did not produce the consistent results obtained from digitalis preparations and the authors find no justification for continued use of either strophanthin or strophosid*

Digitaline nativelle* by mouth was somewhat inconstant in its action in the dosage tried and no support could be found for the contention that this drug is completely absorbed when given orally Intravenously it produced consistently good effects within two hours in a dose of 1 2 or 1 5 mg

Digoxin by mouth produced good results only when dosage was 2 mg or more Given intravenously the drug acted much more rapidly Intravenously digoxin produced a good effect in most cases and a very rapid effect in more than half Lanatoside C 1 5 mg intravenously produced good effect in all cases

Digoxin and lanatoside C were the best drugs for producing rapid digitalization but digitaline nativelle* was scarcely less efficient When necessary to induce digitalization within two hours digoxin 1 5 mg intravenously or 2 3 mg orally and lanatoside C 1 5 mg intravenously only best accomplish desired results To establish adequate digitalization within four hours digoxin 2 mg orally is effective As it is seldom necessary to obtain a digitalis effect in less than two to three hours and since intravenous medication may be less convenient digoxin 2 3 mg orally is generally the best agent to induce rapid digitalization

Maintenance of Adequate Cardiac Output by Regulation of Urinary Excretion of Water and Sodium Chloride, Essential Factor in Genesis of Edema J G G Borst[3] (Univ of Amsterdam) found kidney excretion of

(3) A t me l S and av pp 207 v 1 130

twice weekly for control of rheumatic mitral stenosis with de compensation The liver was 5 fingerbreadths below the costal margin and neck veins were bulging The salt poor diet was continued in the hospital and another injection of mercuhy drin® given On the second day blood urea nitrogen was 98 mg per cent After two more injections of mercuhydrin® the clinical condition was worse Blood chloride concentration was 306 mg per cent Intravenous administration of isotonic sodium chloride solution was started but the patient died while the infusion was being given

The authors believe that nitrogen retention should have suggested dehydration or primary renal disease and either diagnosis should have contraindicated further use of mercurial diuretics or other drastic attempts at dehydration

CASE 2 —Man 47 with decompensated rheumatic heart dis ease was hospitalized because of epigastric pain and anorexia He was given ammonium chloride four times daily and 2 cc mercuhydrin® on the sixth eighth and twelfth hospital days He became dyspneic and toxic and blood urea nitrogen was 88 mg per cent On the nineteenth hospital day blood chlorides were 311 mg per cent Isotonic sodium chloride solution was administered intravenously but next day the patient died

Two other patients on salt poor diets and mercurial diuretics had obvious dehydration In one blood chloride concentration was 285 mg per cent One of the patients died of pulmonary infarction and the other of a cerebral accident In the other three patients the condition was recognized and successfully treated

The authors believe the untoward effects of salt de pletion are often overlooked because of preoccupation with the concept that congestive heart failure can exist only in presence of excessive sodium retention It is sug gested that salt depletion be suspected when weakness lassitude anorexia nausea vomiting restlessness thirst not relieved by water apathy mental confusion blood pressure fall increase in pulse rate diminution in pulse volume clammy skin shock and coma develop in pa tients who have been on low sodium diets and large amounts of mercurials

Lithium Poisoning from Use of Salt Substitutes is re ported by A C Corcoran R D Taylor and Irvine H

one of these components is insufficient the other is still retained Thus in severe forward failure serum concentrations of sodium and chloride may be *increased or decreased*

Effect of an abnormally high cardiac output was studied in one patient with hypoalbuminemic edema by rapid transfusion of 2 L blood which elevated venous pressure from minus 1 to plus 7 cm water This was followed by a 30 fold increase in water and salt excretion one third to one fifth of the water and chlorides of the glomerular filtrate was excreted despite the fact that urea clearance and endogenous creatinine excretion were *unchanged Similar changes of urinary output* occurred after administration of digoxin to a patient with heart failure In both patients high venous pressure in the presence of a normally responding heart resulted in sharp rise in pulse pressure fall in venous pressure and decrease in sodium chloride and water excretion In one patient with paroxysmal tachycardia and polyuria chloride excretion rose during periods of diuresis Intake of 1 L water resulted in diuresis without increase in chloride output Two severely ill patients with peritonitis who had no signs of impaired circulation and who had high pulse pressure and good urea clearance showed nearly total retention of salt and a high blood plasma level of chlorides and sodium

It is concluded that regulation of water and salt excretion is an important factor but only one factor in maintenance of adequate cardiac output

Syndrome of Salt Depletion Induced by Regimen of Sodium Restriction and Sodium Diuresis Louis A Soloff and Jacob Zatuchni[4] (Temple Univ) report seven cases that demonstrate the untoward effects of a regimen of sodium restriction and sodium diuresis in cardiac patients Two of the four fatal cases are given here

CASE 1—Man 52 was hospitalized because of dyspnea nausea and hiccup For many months he had been on a salt poor diet supplemented by injections of 2 cc mercuhydrin®

(4) J A M A 139 1136 1139 Ap 23 19.

Ten were on a low sodium diet and the other 10 received sodium chloride supplements All but one of the animals deprived of sodium were dead at the end of the fourth day and all those given sodium chloride remained in good condition

Biologic Decay Periods of Sodium in Normal Man in Patients with Congestive Heart Failure and in Patients with Nephrotic Syndrome Determined by Na as Tracer During a study of excretion of radioactive sodium conducted primarily to gain information about sodium excretion in heart failure Sam Threefoot George Burch and Paul Reaser[6] (Tulane Univ) established fundamental facts about duration of activity of radioactive substances in the body

The amount of substance introduced into an organism which is excreted at any one time has a fairly constant relationship with amount of the substance in the body According to mathematical calculations substance are never completely eliminated Practically it is valuable therefore to measure the interval required to eliminate one half the material known as the biologic half life period of the substance Since this period equals time required to excrete one half the total amount of the regular form of the substance already in the organism measurement of biologic half life period indicates total rate of turnover of the regular substance This knowledge enables one to know duration of exposure of the organism to specific radiation and is important in determination of safety measures in use of these substances It is also necessary in planning experiments in which radioactive substances are used

The following data indicate that biologic half life of a substance for a normal organism cannot be applied empirically to an abnormal one Continuous observations of blood concentration and urine excretion of radioactive Na were made for 20 70 days on four normal subjects six patients with heart failure and two in the nephrotic stage of chronic glomerulonephritis

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(6) J L b & Cl M d 34 1 13 J y 1949

Page[5] (Cleveland Clinic) Among seven patients with lithium intoxication observed by the authors two died lithium intoxication appeared to be a contributory cause of death The salt substitute used by these patients was westsal ® a solution of lithium chloride with citric acid and a small amount of potassium iodide The syndrome observed was characterized by tremor muscular and re flex hyperirritability confusion and coma Electroen cephalographic abnormalities were demonstrable

Similar symptoms were reported over 35 years ago by a Cleveland physician who took 2 Gm lithium chloride after each meal for three meals and an additional dose at bedtime Since symptoms developed in the authors patients on much smaller doses of lithium chloride it seems likely that sodium restriction increases suscepti bility to lithium toxicity Though action of lithium on muscle and nerve metabolism has not been studied thor *oughly lithium is thought to replace sodium in sodium* depleted persons

The authors Case 3 is reported here

Man 47 with severe essential hypertension was placed on a low sodium diet supplemented with westsal ® For the first four weeks 6 Gm sodium chloride daily in enteric coated capsules was given for control observations on the effects of low sodium diet For several weeks after withdrawal of sodium chloride supplement the patient s control of salt intake was erratic During this period muscle twitches appeared transiently These with insomnia depression apathy and fatigue reappeared three weeks after he agreed to maintain severe sodium restriction The symptoms disappeared four days after use of westsal® was discontinued although sodium restriction was maintained

The course of events indicated that use of westsal® as a salt substitute causes toxic symptoms during periods of severe sodium restriction Use of salt substitutes in low sodium diets should not go unsupervised In addi tion to toxicity of lithium chloride potassium present in some salt substitutes may be toxic to patients with renal insufficiency

Addendum —The effect of sodium depletion on lithium toxicity was investigated by G Masson in 20 animals

(5) J A M A 139 685 688 Ma 12 1949

compound has shown that it can overcome arrhythmias produced by mercurial compounds However at the same time the diuretic effect of the mercurial is lost In an attempt to preserve the detoxifying effects of BAL and to avoid its antidiuretic effects a monosulfhydryl MT 6 was added to mercuzanthin® The resulting compound was called thiomerin® This substance was found to be so nonirritating that it could be injected subcutaneously without untoward effect and so nontoxic that it could be given in doses 160 times the maximal tolerated dose of mercuhydrin® without producing electrocardiographic changes Thiomerin® was then put in the hands of the authors for clinical investigation

It was injected subcutaneously in 100 cardiac patients and intravenously in 50 patients with no serious reactions Electrocardiograms taken during and at one minute intervals after intravenous injections showed no significant cardiac arrhythmias In three patients moderately severe pain occurred at the injection site and four patients had temperatures of 102 103 F and one a temperature of 104 F The fever may have been due to pyrogens in distilled water Thiomerin® was given in 2 cc doses subcutaneously for five days in succession without untoward reactions or signs of myocardial or renal irritation

Diuretic responses were not equal to those of other mercurials in the first 24 hours but usually were more persistent and during the course of two or three days the patients lost 1 15 lb (average 3 lb) Urinary output increased from 1 5 to 6 L with an average of 4 L in the first 24 hours

Ammonium chloride increased diuretic effectiveness of thiomerin® so that 0 5 or 0 75 cc doses were often effective

Circulatory and Diuretic Effects of Theophylline Isopropanolamine were investigated by D M Fowell (Stockton Calif) J A Winslow V P Sydenstricker and N C Wheeler[8] (Augusta Ga) Cardiac output was

(8) A h I t M d 83 150 157 F brn y 1949

In the controls serum concentration of sodium dropped to half the initial level in 12 14 days For no apparent reason rate of elimination of the isotope in urine was such that half the sodium administered was excreted only after an average of 28 8 days In two patients slowly recovering from heart failure the period necessary for reduction of serum concentration of sodium to half the initial level was about three times as long as in controls rate of urinary excretion of sodium was less than half that in controls In two patients rapidly *improving from heart failure sodium* was eliminated more rapidly than in those slowly improving In two patients becoming worse it took longer *to* excrete sodium than it did in controls or in patients rapidly improving from heart failure but essentially the same time required by patients who were slowly improving In two patients with the nephrotic syndrome decline of serum *concentration of sodium was less than one* fourth as rapid as in controls and rate of urinary elimination was one tenth to one twentieth as rapid

Factors other than the biologic half life period of the substance can alter its excretion Such influences are fixation of the substance in the body and alterations in fluid output

Treatment of Myocardial Failure Studies of New and Safe Diuretic—Thiomerin® George R Herrmann John W Chriss Milton R Hejtmancik and Paul M Sims[7] (Univ of Texas) point out that organic mercurial salts are generally accepted as the most efficient diuretics Deaths among patients taking mercurial diuretics *led to* studies on animals which showed that organic mercurials in common use produced direct toxic action on the heart and consequent conduction changes Auriculo ventricular dissociation interventricular blocks broadening of the QRS complexes ventricular tachycardia fibrillation and standstill have been found In an attempt to find a less toxic mercurial diuretic mercuhydrin® was produced Recent work with BAL a double sulfhydryl

(7) Te Stat J M d 45 798 Febru ry 1040

the e disorders Restriction of total caloric intake is probably at least equally important.—Ed

Dietary Cholesterol Its Role in Atherosclerosis Bernard A Sachs (New York City) reviews evidence supporting the concept that exogenous cholesterol influences development of atherosclerosis In several diseases both hypercholesteremia and extensive atherosclerosis occur Best known of these conditions are hypothyroidism diabetes mellitus kidney disease and essential xanthomatosis a familial disease characterized by skin xanthomas hypercholesteremia and coronary artery disease in children and young adults

Atherosclerosis has been produced in many experimental animals by feeding cholesterol In these animals blood cholesterol levels are often raised however atherosclerosis can be produced by feeding such small amounts of cholesterol that hypercholesteremia does not develop

Transient hypercholesteremia which reaches its peak in four hours has been observed in man after ingestion of foods containing cholesterol After such foods are administered for a long period persistent elevation of serum cholesterol occurs Atherosclerosis has been associated with both high fat and high protein diets in man Extensive atherosclerosis has been reported in a tribe of nomads whose daily diet contained 20 L milk and 4 5 9 kg meat Some observers believe that the condition was more prevalent in diabetics when high fat diets were used Diet histories taken from 50 men with myocardial infarction revealed excessive cholesterol intakes Review of a large series of necropsies showed atherosclerosis to be more common in fat persons

The Chinese whose diet contains little cholesterol rarely have atherosclerosis The same is true of Okinawans Javanese and Costa Ricans Incidence of cholesterol deposits in the aorta is reported to have decreased during a period of fat famine in Germany during World War I

[illegible]

studied by means of catheterization of the right side of the heart before and at 2 or 3 minute intervals for 30-40 minutes after slow intravenous injection of 0 5 Gm theopropanol* in 15 patients with heart disease Diuretic action of the drug was studied in 21 patients 19 in heart failure and 2 with cirrhosis Most of the patients with heart failure had had unsuccessful trials of digitalis Diuretics were withheld for three days before theopropanol* was given

Cardiac output consistently increased after administration of theopropanol* The increase lasted about 15 minutes and averaged 30 per cent Both heart rate and stroke volume increased despite the fact that right ventricular filling pressure decreased The drug acted as a respiratory stimulant and increased pulmonary ventilation and oxygen consumption

No diuretic effects were noted when the drug was given intravenously but they were produced by intramuscular or oral administration Of 20 patients given 0 4 Gm three times daily orally 11 manifested toxic effects With a 0 2 Gm dose three or four times daily only 1 of 20 patients had nausea Diuretic effect of the smaller dose was as satisfactory as that of the larger Of 21 patients given theopropanol* orally 12 showed good diuresis i e 24 hour volume of urine was more than doubled Diuretic response was satisfactory in 11 of 14 patients with congestive heart failure of arteriosclerotic origin and in 1 of 2 patients with hepatic cirrhosis but responses of patients with rheumatic heart disease and hypertensive nephritis were not satisfactory

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ARTERIOSCLEROSIS

The evidence that arteriosclerosis is related to cholesterol metabolism may be regarded as conclusive However the relative roles of dietary intake synthesis destruction and excretion remain uncertain *Pending* more definite information it is desirable to restrict *cholesterol* in the diet of persons with hypercholesteremia hypertension or coronary disease or with a pronounced family history of

these disord rs Restriction of total caloric intake i probably at least equally important —Ed

Dietary Cholesterol Its Role in Atherosclerosis Bernard A Sachs[2] (New York City) reviews evidence supporting the concept that exogenous cholesterol influences development of atherosclerosis In several diseases both hypercholesteremia and extensive atherosclerosis occur Best known of these conditions are hypothyroidism diabetes mellitus kidney disease and essential xanthomatosis a familial disease characterized by skin xanthomas hypercholesteremia and coronary artery disease in children and young adults

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Though many theories have been proposed to explain the pathogenesis of atherosclerosis Sachs is most interested in that proposed by Gordon who hypothecates that Kupffer cells are released from the reticuloendothelial system into the blood stream where they engulf fat and then penetrate the endothelial linings of blood vessels After deposition connective tissue growth is stimulated It is postulated that the disease does not affect small blood vessels because their blood flow is not high enough to push Kupffer cells into the blood vessel wall and lack of intermittent flow in these vessels does not favor movement of Kupffer cells out of the center of the blood column

Predilection of atherosclerosis of the aorta for the bifurcation has been attributed to the greater intermittency of blood flow here with consequent disruption of axial and marginal streams Predilection for the coronary arteries has been related to the great thickness of the intima of these vessels

Though atherosclerosis occurs without hypertension it is rare for hypertension to occur without atherosclerosis Familial incidence of atherosclerosis may be the result of hereditary disturbance of lipid metabolism or of dietary habits Foods high in cholesterol are egg yolk brain butter cream oysters sweetbreads milk cheese and animal fat Adults on fat poor diets consume *39 109* mg cholesterol on average diets *200 362* mg and on high fat diets up to 1 400 mg

Recent Advances in Study of Arteriosclerosis are outlined by S O Waife[3] (Univ of Maryland) The relation of nutritional status and obesity to arteriosclerosis has been studied by many investigators Arteriosclerosis is about twice as common in the obese as in poorly nourished persons Obesity alone cannot be said to cause arteriosclerosis however since almost 40 per cent of a group of poorly nourished persons over age 75 had severe atherosclerosis at autopsy Study of 22 000 army officers showed hypertension more common a overweight

(3) A I t M d 30 635 645 Ma h

persons and weight loss was accompanied by reduction in blood pressure in three fourths of a large series of patients Among 80 patients under 36 with fatal coronary arteriosclerosis 91 per cent were obese

Attempts to produce cerebral arteriosclerosis in animals have met with little success Study of 18 brains of patients over 77 revealed scattered areas of cortical atrophy in all No pathognomonic abnormalities were found however Among 2 000 patients studied at autopsy in a state hospital psychosis from cerebral arteriosclerosis was diagnosed in 25 per cent Incidence of abnormal electroencephalograms was higher in patients with cerebral arteriosclerosis and senile psychosis than in older patients with functional psychiatric disorders Roentgen visualization by injection of thorium dioxide into the internal carotid artery contributed much to the study of cerebral circulation

Personality of the patient with coronary occlusion has been described as one of compulsive devotion to work with a compelling desire to surpass persons in a superior position Such patients dislike sharing responsibility and are given to brooding

Studies of coronary atherosclerosis have shown that this condition is more common in the presence of hypertension and/or faulty cholesterol metabolism Autopsies on 24 infant who died at birth revealed that the coronary intima is unusually thick in the male and even at birth is about three times thicker than the coronary intima of the female Although there is disagreement as to presence of an unusual clottin tendency in persons with coronary occlusion the favorable effect of dicumarol* on myocardial infarction has been established Whether effort is a precipitating factor in myocardial infarction continues to be a source of argument

The value of sympathectomy in treatment of arteriosclerosis of the lower extremities also continues to be disputed Cigaret smoking has been found to cause arteriolar constriction with diminished blood flow in older patients, but to less extent than in younger patients In

cidence of thrombosed peripheral arteries was higher in smokers than in nonsmokers Moenckeberg s sclerosis is a rare condition occurring in young and middle aged men with x ray evidence of calcification of peripheral vessels but no sign of impaired circulation Two new sug gestions have been made for treatment of peripheral arteriosclerosis (1) dramatic relief of intermittent claudication by intramuscular and intravenous injection of ether and (2) excellent results from administration of histidine and ascorbic acid in order to elaborate his tamine in vivo have been reported

Metabolism of cholesterol remains obscure The level of free cholesterol in plasma effects rate of mobilization of fatty acids from their depots and rate of phospholipid synthesis Surprisingly feeding of cholesterol and vita min E retards development of periarteritis in dogs on high fat diets Conversely in rabbits parenteral admin istration of vitamin E appreciably augments deposition of cholesterol in the aorta Other experiments have dem onstrated that serum colloids of dogs and rabbits on high cholesterol diets are more labile than normal For many years it has been known that thyroid extract and iodides reduce incidence of arteriosclerotic lesions but a more recent report indicates that use of iodide does not protect thyroidectomized animals from atherosclerosis

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ARRHYTHMIAS

The following abstracts emphasize the responsiveness of cardiac irregularities to treatment Since the different arrhythmias require different management their recognition is of great practical im portance —Ed

Variable Loudness of First Heart Sound in Auricular Fibrillation David A Rytand[4] (Stanford Univ) made phonocardiographic tracings throughout 38 160 cycles of the heart in 12 patients with auricular fibrillation to establish a clinical sign previously given little attention

(4) Am. H rt J 37 187 204 F b u ry 1949

—variation in intensity of first heart sound in auricular fibrillation This variability occurs in another condition characterized by variations in auriculoventricular interval complete heart block In phonocardiograms peak amplitude of first heart sound was converted into arbitrary units and plotted against the interval between second heart sound of the preceding cycle and onset of first heart sound

In five patients without mitral stenosis first heart sound had greatest amplitude when it came 0 12 0 24 seconds after the preceding second sound Amplitude of first heart sound fell during the next tenth of a second to about one third of its maximum magnitude Peak amplitude with longer diastolic periods remained diminished or had a secondary zone of accentuation These changes of peak amplitude were similar to those in patients with complete heart block and are further evidence that first heart sound is louder when onset of ventricular systoles finds the auriculoventricular valves wider open even though strength of contraction is weaker

In seven patients with mitral stenosis there was little variation in peak amplitude of the first sound Variability in intensity of first heart sounds in auricular fibrillation therefore is a point against presence of mitral stenosis

Abnormal Rapid Rhythms Associated with Digitoxin Therapy Harold D Levine[5] (Boston) reviewed records of 338 patients given digitoxin and 534 patients given digitalis leaf at Peter Bent Brigham Hospital Toxic abnormal rhythms occurred in 2 per cent of patients given digitoxin and 0 9 per cent of those given digitalis leaf This difference was not statistically significant but the clinical impression remained that with digitoxin rapid rhythms developed more insidiously than with leaf because of absence of nausea vomiting and diarrhea with the newer drug

Of the seven patients in whom toxic rhythms developed during administration of digitoxin three had re

ceived the drug in amounts generally considered not to be excessive Cause of such abnormal rhythms in patients given these drugs is not clear Idioventricular rhythms auriculoventricular dissociation and ventricular tachycardia were all regarded as different degrees of increased irritability of the ventricles

Though in some instances the physician will be unable to decide whether a rising heart rate is the result of progression of disease or of digitalis poisoning in many the two can be differentiated Sudden change from a totally irregular to a regular rhythm should suggest digitalis intoxication Though cardiac rhythm may revert from auricular fibrillation to a normal sinus mechanism under digitoxin therapy fundamental action of digitalis bodies favors perpetuation rather than termination of this arrhythmia Patients whose rhythms suddenly become regular should therefore have electrocardiograms to determine if they have idioventricular rhythm with complete auriculoventricular block or auriculoventricular dissociation Digitalis can cause auricles and ventricles to beat independently by depressing auriculoventricular conduction and permitting ventricles to beat with their own rhythm or it may increase irritability of ventricles so that they run ahead of the auricles despite normal auriculoventricular conduction

Levine does not disparage digitoxin but advises that during its use the physician be on the alert for evidences of intoxication

Action of Neostigmine in Supraventricular Tachycardias was studied by Samuel Waldman and Louis Pelner[6] (Brooklyn) Vagus nerves are cardioinhibitory in action slowing of the heart is achieved mainly by lengthening of diastole systole is little affected The right and left vagus nerves differ in action Stimulation of the right nerve results mainly in slowing the auricular beat and thus reduces ventricular rate Stimulation of the left nerve causes ventricular slowing by depressing auriculoventricular conduction Neostigmine by inhibit

(6) An Int. Med 29 53 63 July 1948

ing the action of cholinesterase at the myoneural junction permits choline to exert its full effect In sinus tachycardia neostigmine decreases the rate of impulse formation at the sinoauricular node as evidenced by an increased T P interval In paroxysmal auricular tachycardia the ectopic focus is somewhere in the auricle not in the sinoauricular node Therefore neostigmine apparently acts in this condition by allowing the left vagus nerve to decrease auriculoventricular conduction In paroxysmal nodal tachycardia again the left vagus nerve effect is the predominant factor Tachycardias in general are probably produced by autonomic nervous system imbalance and neostigmine by correcting imbalance through vagal action restores the heart to normal rhythm

The authors report five cases in which neostigmine was administered two of which follow

CASE 3—Girl 20 known to have rh umatic heart disease had had frequent recurrent attacks of palpitation at times lasting several davs Examination revealed tachycardia of 166 The electrocardiogram showed typical paroxysmal auricular tachycardia Carotid sinus and ocular pressure had no effect Neo tigmine 1 mg wa given intramuscularly In five minutes heart rate fell to 94 100 the P R interval was 0 36 second In 15 minutes heart rate was 71 and the P R interval 0 22 second Becau e of frequently recurring attacks an attempt at prophylaxis was made Digitalization failed to prevent attack quinidine diminished their frequency Neostigmine bromide 0 015 Gm orally three times daily at equal intervals has been u ed since October 1945 and the patient has had only a few short lasting attack No attack wa severe enough to require additional medication

CASE 5—Woman 22 known to have rheumatic heart disea e had had recurrent attacks of palpitation for two or three years Pulse rate was 136 The electrocardiogram showed nodal (probably midnodal) tachycardia Injection of 1 mg neostigmine reduced the rate to 115 in five minutes A P wave appeared with a P R interval of 0 21 second A slight first degree block was produced In 10 minutes the rate was 100 and P R interval 0 18 second In 15 minutes the rate was 88 with P R interval of 0 16 second

Neo Synephrine[*] in Treatment of Paroxysmal Supraventricular Tachycardia William B Youmans Morton

J Goodman and Jarvis Gould[7] (Univ of Oregon) report that within 35 70 seconds after rapid intravenous injection of neo synephrine® in nine patients with paroxysmal supraventricular tachycardia sinus rhythm was restored to normal in seven Most attacks were reverted by 1 mg or less It is thought that use of rapid acting vasopressor substances will prove the preferred treatment in this condition The drug is believed to act by suddenly increasing blood pressure in the carotid sinus and thereby reflexly affecting heart action

In some patients rhythm reverted to normal after only enough neo synephrine® to increase blood pressure suddenly from the subnormal level present during the attack to the patient s normal level This suggests that low blood pressure secondary to tachycardia may perpetuate the attack In each case the dose of neo synephrine® was diluted so that it could be injected in 20 30 seconds During the period when normal sinus rhythm occurred systolic blood pressure was rapidly rising The initial dose should not exceed 0 5 mg and larger doses may be used when necessary after blood pressure has returned to its preinjection level a period not exceeding 10 minutes in the patients studied

There were no unpleasant symptoms Many patients noted tingling of the skin apparently from vasoconstriction and piloerection The only failures occurred in two patients in whom attacks developed postoperatively It is suggested that insufficient blood pressure rise was produced In most cases paroxysmal supraventricular tachycardia ceased when systolic blood pressure reached a level of 160 mm Hg or less

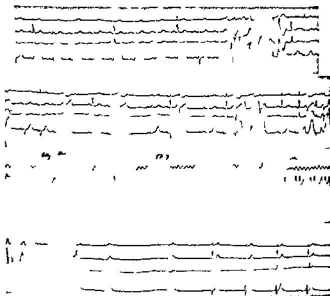
Neo synephrine® is less effective as a pressor agent when blood volume is low Its action may be counteracted by use of vasodilator or adrenolytic drugs including barbiturates which produce vasodilatation and decrease carotid sinus sensitivity

Case of Morgagni Adams Stokes Attacks Caused by Transient Recurrent Ventricular Fibrillation without

(7) Am H art J 37 359 373 M ch 1949

Apparent Organic Heart Disease is described by Torjus Moe[8] (Oslo) This is thought to be the first well estab lished case of paroxysmal ventricular fibrillation with syncope in a patient with a normal heart

Man 38 was ho pitalized because of attacks of palpitation for almost a year and two recent epi odes of fainting He had



Fg 94—Aft n bythm d d f med ent cula ompl es ECG h w ent cula fib llation d then b dyca d nd cul t cul by hm. Th d fferent p rt f t g f llow co ly pt f som seconds j st bef p t ent b d Adams-Stokes tta k. Wh n h f ted lect oca diogr ph w immediately w tched on g (Courtesy f Moe T Acta med. Sca d na 130 416 435 1948)

not had rheumatic fever or chorea and had never been dyspneic or had swelling of the legs He fainted three or four times while being examined. Between attacks of syncope heart rate was 70 90/minute with many extrasy toles Just before attacks the pul e suddenly topped and after the patient was pul eless for 8-10 second he lost con ciousness Electrocardiograms taken immediately before during and after one of these at

(8) Acta me l Scand na 130 416 435 1948

tacks (Fig 94) showed that after sinus rhythm with extrasys toles there was a period of ventricular fibrillation followed by sinus bradycardia and auriculoventricular rhythm

Epinephrine was given during the attack but when the ECG was developed it was decided that quinidine should be administered Quinidine 0 2 Gm was then given per os and 0 6 Gm was given four hours later In seven hours a total of 1 Gm quinidine was given and syncope did not recur

Physical examination chest x ray and other laboratory work failed to reveal any abnormality suggesting heart disease Quinidine administration was continued and the patient had no further attacks of syncope

Adams Stokes attacks may result from ventricular standstill during auriculoventricular block or from disturbance in the production of impulses which results in ventricular tachycardia or ventricular fibrillation Sinus block and sinoauricular block seldom lead to Adams Stokes attacks *During an attack it may be impossible to differentiate ventricular standstill from ventricular fibrillation but since treatment of these two disturbances is so different it is important that the differential diagnosis be established between attacks* The patient with auriculoventricular block usually has a regular cardiac rhythm of 30 40/minute whereas the patient who is prone to ventricular fibrillation may have ventricular extrasystoles between attacks In ventricular standstill the heart should be stimulated by epinephrine caffeine or thumping on the chest wall In ventricular fibrillation quinidine is the treatment of choice to diminish ventricular irritability

Mechanism of Irregular Sinus Rhythm in Auriculo ventricular Heart Block was studied by Irving R Roth and Bruno Kisch[9] (New York City) It has long been known that in auriculoventricular heart block the auricles often exhibit an irre ular rhythm Auricular intervals which embrace ventricular systoles are usually the short e t whereas those which follow in the wake of a ventricular systole are the longest The irregularity is es

(9) Am H a t J 36 57 76 A g t 1948

sentially a sinus arrhythmia characterized by postsystolic slowing of the auricles This slowing varies with degree of block

During the past 40 years many theories have been proposed to explain the irregularity of auricular activity in auriculoventricular heart block In recent years it has become more apparent that a reflex vagus effect postulated by earlier observers is a factor in production of auricular arrhythmia in this type of block The authors have accumulated evidence that postsystolic auricular slowing in auriculoventricular heart block is the result of a reflex vagus effect initiated by the arterial pulse The physiologic mechanism proposed is that of reflex inhibition of the auricular pacemaker initiated by pressure rise within the aorta and carotid arteries incident to the systolic injection of these vessels Such an aortic and carotid sinus reflex alone it would seem accounts for the fact that the auricular slowing in heart block usually appears in cycles immediately after ventricular systole and for the fact that during longer periods of ventricular standstill the slowing vanishes gradually over a succession of several cycles Duration of the P P interval is influenced therefore by the proximity of adjacent ventricular complexes Tone of the vagus nerves is known to depend to some degree on the pressure within the aorta and carotid artery Increase of pressure within these vessels raises vagus tone and lowers tone of its sympathetic antagonist In support of this hypothesis it was found that the auricular wave was influenced only by ventricular systoles which significantly increased pressure in the aorta

Since the aortic carotid sinus reflex is influenced by age resiliency of arteries blood pressure pulse rate sensitivity of nerves and nerve centers and the nutritional state and anatomic integrity of the sinoauricular node it is obvious that the effects of ventricular systole on auricular activity will be different in various persons with auriculoventricular heart block

Treatment of Heart Block with Adrenergic Substances E Roelsen[1] (Silkeborg, Denmark) during four years treated seven patients with different forms of heart block by administration of epinephrine The drug is considered of value in patients with heart block because of its ability to stimulate the ventricular pacemakers and to sensitize the auriculoventricular conduction bundle

In one of Roelsen s patients complete auriculoventricular dissociation with bradycardia and finally ventricular standstill yielded promptly to 0 5 mg epinephrine given subcutaneously A *normal rhythm* was produced and maintained for two years by administration of 25 mg amphetamine daily Death finally occurred from noncardiac disease

In another patient complete auriculoventricular block developed during acute coronary occlusion There was pronounced shock with numerous attacks of syncope because of ventricular standstill demonstrated electrocardiographically Attacks were stopped by injection of epinephrine and a basal rhythm was established by use of the drug About 32 hours later rhythm was normal and the subsequent course was uneventful

Because larger doses cause ventricular extrasystoles the dose of epinephrine recommended is 0 5 mg subcutaneously or in more severe cases 0 05 mg intravenously In desperate cases 0 25 mg may be injected into the heart

Epinephrine is of course contraindicated in the presence of ventricular fibrillation

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ELECTROCARDIOGRAPHY

The tendency to base specific etiologic diagnosis on changes in the electrocardiogram is to be strongly deplored This valuable tool often reveal disturbances in th electric functions of the heart such functional disturbances may or may not be attended by demonstrable structural alterations The decision as to the cause

(1) A ta m d S a d av 132 534 555 1949

of an abnormal electrocardiogram must be based on the clinical picture Attempts to interpret the electrocardiogram without knowl edge of the clinical findings are likely to result in grave errors — Ed

Newer Aspects of Clinical Electrocardiography are reviewed by Richard Gubner and Harry E Ungerleider (New York City) The QRS complex represents the stage of myocardial excitation or depolarization and the S T segment and T wave represent repolarization or re turn to the resting state Excitation of the ventricles is instituted by impulses in the Purkinje network located in the subendocardial regions of the ventricles Impulses then spread directly through the ventricular walls to the external surface The electrocardiogram represents chiefly the electric activity of the free wall of the left ventricle Current traveling toward the electrode records a positive deflection and that traveling away from the electrode a negative deflection An electrode on the left arm therefore normally records a positive deflection and an electrode on the right arm a negative deflection

In right bundle branch block the impulse travels pre dominantly from left to right and records downward de flection in the electrode on the left arm (leads I V_1 and V_2) In left bundle branch block the impulse travels predominantly from right to left and records positive deflection in these leads

When the heart lies transversely the left arm poten tial (lead I) is more strongly positive than when it is in normal position and the left leg (lead III) now not faced by the free left ventricular wall has a small or negative potential Conversely when the heart lies ver tically the free left ventricular wall faces the left leg so that there is positive deflection in lead III

The Q wave is merely a recording of the normal neg ativity of the interior of the ventricular cavity through the window of infarcted myocardium This wave may be found in lead I if anterior infarction extends high enough so that part of the window points toward the left arm In posterior infarction the window usually points

to the left leg and Q is inserted in lead III To detect Q waves which may not be found in these leads the authors routinely use six precordial leads in patients suspected of having myocardial infarction In place of the esophageal lead to detect high posterior infarctions they use an electrode on the back between the left scapula and left side of the diaphragm In addition leads CR_1 and CR_2 are used in patients with arrhythmias

Unipolar or V leads have been of great theoretical interest but are of practical value only in evaluation of Q_3 The Q_3 from infarction produces a Q wave in the unipolar left leg lead but this does not occur in the Q_3 which results from hypertension or from transverse position of the heart in obesity Low T Q greater than 1 mm or absence of S_1 in standard leads suggest that Q_3 is the result of infarction

Study of ECG s of 50 persons with nonfatal myocardial infarction and 50 persons with fatal infarction showed that bundle branch block was more common in patients who failed to survive Other grave prognostic signs included deep Q_1 or low R_1 with deep S_2 and S_3 in patients with anterior infarction and marked S T deviation particularly in precordial leads and T_1 changes in patients with posterior infarction

Left ventricular hypertrophy may be considered to be present when left axis deviation occurs with a QRS higher than 2 5 mm with any depression of S T_1 or T_1 lower than 1 mm

For detection of coronary artery disease ECG s should be made at frequent intervals during the 10 minutes after the patient has climbed two steps or mounted a kitchen stool 20 30 times in 1½ 2 minutes Coronary artery disease may be revealed by finding S T depressions and T wave changes in the tracings

Abnormal Electrocardiograms in Absence of Demonstrable Heart Disease Among 5 000 ECG s David Littmann[3] (West Roxbury Mass) found 9 in which there were abnormalities of T waves particularly in the

(3) Am J M S 5 337 350 Sept mber 1948

thoracic leads in patients in whom heart disease could not be proved Eight patients had no symptoms referred to the heart and in the ninth patient symptoms referred to the heart may have been functional

In the first patient the ECG revealed alternating ventricular premature beats with inversion of T waves in lead IV F in the complexes representing sinus beats Subsequently when extrasystoles became fewer it became obvious that the anomaly occurred only after premature beats and was in some manner associated with them It is hypothecated that alterations in cardiac filling caused the T wave abnormalities in this patient

In two patients ECG s revealed what was interpreted as persistence of the juvenile pattern i e normal limb leads but diphasic or inverted T waves from CF through CF_6 usually only in the leads nearest the sternum

In four patients limb leads contained T wave variations from lowering and flattening to frank inversion The most spectacular abnormalities in these patients were noted in thoracic leads however The greatest degree of inversion of the T wave occurred at or near the apical position in contrast to the abnormality in the patients just described QRS complexes and S T segments were normal and in all subjects essentially normal curves were obtained after the passage of time or vigorous exercise Since direction of the T wave is thought to depend on slight but constant asynchrony of the terminal electric phenomena of the ventricles it is postulated that some normal hearts fail to have the same degree of ventricular asynchronism but instead exhibit an unstable equilibrium which manifests itself in variations in direction of the T wave Another possibility is that some normal persons have an unusually labile or exaggerated asynchronism of the terminal portion of the ventricular complex It is suggested that these patients have normal hearts with normally unstable T

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(3) Am J M d 5 337 350 S ptembe 1948

this abnormality is seen technical error should be sus pected

In one of the author s patients with hypertension and angina pectoris an ECG taken just before discharge from the hospital revealed a deep Q with a high S T take off in leads II and III with corresponding depres sion of S T in lead I Posterior wall infarction was sug gested but closer inspection showed that the QRS com plex in the third and especially in the second lead had a peculiar straddling form In addition there was a sug gestion of a small R in lead III Thus there was no deep Q in lead III but a deep S When similar ECG s were received for two other patients without clinical evidence of myocardial infarction the ECG apparatus was investi gated and a break in a wire for the left leg lead was found to have been concealed by the insulating sheath Control ECG s for these patients were normal

Break of current to the right arm gives ECG s re sembling those in anterior wall infarction both for pa tients with left ventricle hypertrophy and for those with normal hearts Break in current to the left arm merely gives a somewhat featureless lead I and a slightly altered lead III but no particular pathologic changes

The reason why broken current ECG s can occur at all is that the entrance grid of an amplifier with in terruption of the incoming current has no definite po tential and capacitive influences may come into force from the other currents when the amplifiers have a very high entrance impedance The phenomenon can be elim inated by coupling in a resistance of about 0 5 megaohm between each of the intakes for the currents to the left arm left leg and apex cordis on the one hand and the intake for current to the right arm on the other hand The reduction of entrance impedance produced has no influence in ordinary electrocardiography

Right Precordial Lead Recent studies in clinical elec

leads CF CF$_3$ CF$_4$ CR$_2$ and CR$_3$ Normal ECG s could be made just after the patient wakened in the morning A continuous ECG made during distention of the stomach with air showed that as the stomach became distended the T wave was first depressed and then inverted The ECG became normal again when the stomach was deflated

The last patient was hospitalized with spontaneous pneumothorax demonstrated by x ray ECG made shortly after hospitalization showed a low T$_1$ no R$_4$ and slightly inverted T$_4$ ECG s made later showed flat to inverted T waves and no R waves in the CF leads made in supine position In erect and prone position T waves in all the CF leads were erect but R waves remained small Cause of this phenomena was thought to be the physical effect of air in the mediastinum and the pleural space lying between heart and chest wall on the left This produced a region of diminished conductivity and interfered with the normal ECG When the patient was erect or prone air was no longer trapped between heart and exploring electrode part of the nonconducting medium was removed and the tracing became normal

Technical Errors in Taking of Electrocardiograms and Consequent Misinterpretation are considered by Torjus Moe[4] (Oslo) Technical errors most frequently resulting in misinterpretation of the ECG are chiefly those in which electrodes for the different leads are interchanged and those in which there is failure to make contact at one of the leads where it attaches to the skin or interruption of one of the leads itself

Before diagnosing situs inversus electrocardiographically one must always make sure that the arm electrode has not been misplaced This mistake arises because the technician stands with her right arm turned toward the patient s left or vice versa It is natural to mistake the patient s right for the technician s left In all such wrongly connected ECG s I QRS and T waves are deflected in a direction opposite to the normal When

(4) Acta m d S a d n 130 515 5 4 1948

occurrence of a posterior myocardial infarction and revealed the development of characteristic changes These changes in CF_1 were found in each of 35 cases of recent infarction of the posterior wall The CF_1 cardiographic changes were of opposite sense to those observed in the unipolar left leg lead in this condition and may be contributed at least in part by the left leg component R became taller and S deeper RS T was often depressed below the base line The most striking alteration was in the T wave which was positive in all such cases though in normal persons T was positive in only 12 per cent

The authors suggest that T wave alteration in CF_1 could be of use in diagnosis of recent posterior myocardial infarction It may be particularly helpful when changes in limb leads are equivocal or absent A negative T wave in CF_1 would seem on the basis of this study to be important evidence against recent posterior infarction

Clinical Intoxication with Potassium Its Occurrence in Severe Renal Insufficiency was studied by Norman M Keith and Howard B Burchell[6] (Mayo Clinic) In 1939 a group at Mayo Clinic attempted to correlate concentration of serum potassium and development of electrocardiographic changes Changes previously reported were confirmed in one patient with uremia who died 24 hours after electrocardiograms were made Death was attributed to cardiac standstill from potassium intoxication Within the next seven years hyperpotassemia was detected in 13 of a large group of uremia patients Clinical diagnosis of nephritis was confirmed at autopsy in 10 Potassium salts were administered as diuretic agents to three of these patients in two toxic effects resulted It is clear that administration of potassium salts to patients with severe renal insufficiency may be dangerous

Despite other reports of flaccid paralysis of extremities in potassium intoxication no objective neurologic abnormalities were detected in the authors patients

(6) Am J M S 217 1 1 J ry 1949

precordial lead C_1 is recommended for general use sufficient data have not yet been obtained on this lead either in regard to the range of normal or to its various abnormalities In an attempt to gain further information on the right precordial lead C_1 and to assess its value for general use Harry Vesell and Benjamin Shorr[5] (Beth Israel Hosp New York City) reviewed previous reports in which this lead was used took a series of electrocardiograms including this lead on patients without heart disease to determine the range of normal variations and noted characteristic alterations in CF_1 in certain cardiac conditions particularly posterior wall infarction in which use of this lead may be helpful

The following is an analysis of the normal variations of the precordial ECG taken in right pectoral position CF_1 in 265 adults without heart disease ECG s were taken in both sitting and recumbent positions P waves were negative in 88 per cent diphasic in 9 per cent and positive in only 3 per cent Average negative P was — 1 3 mm Q waves were not observed in any patient R waves were absent in 13 (monophasic negative QRS wave) QRS duration was the same as in CF_4 or limb leads RS T segment was often elevated up to 1 8 mm RS T depression was not seen T was negative in 183 diphasic in 46 and positive in only 34 In 15 cases in which T was negative with the patient sitting, a tracing was also taken the same day with him recumbent In all 15 T remained negative with little variation in depth No correlation of T wave negativity with deviation of the electric axis of QRS was noted When 123 tracings in which a Q wave was present in limb lead III were examined no correlation was noted with respect to T in CF_1 both negative and positive T waves being observed Thus in normal subjects a negative T in CF_1 may occur with a prominent Q III In 15 cases with the cardiographic pattern of left ventricular strain T was upright in CF_1 in 14 and diphasic in 1

In two patients CF_1 was taken before and after the

(5) B t H t J 10 158 164 J ly 1948

particularly hypertension and aortic valvular disease occurred in 72 per cent and a pronounced left ventricular enlargement occurred with about the same frequency Local damage to the left bundle branch was found in 14 patients Most of these had myocardial infarction

The study indicates that left bundle branch block revealed by ECG is five times more often due to enlargement of the left heart than to a local lesion of the left branch of the bundle In such conditions dilatation is thought to be more important than hypertrophy It is suggested that ECGs of left ventricular hypertrophy and of left bundle branch block represent different degrees of retarded conduction to the left heart In both there is pronounced left ventricular enlargement The authors believe that present terminology is inadequate and that the two terms in use should be replaced by ECG of left sided retardation Bundle branch block represents the most extreme grade of this condition

Transient Ventricular Fibrillation Prefibrillary Period during Established Auriculoventricular Dissociation with Note on Phonocardiograms Obtained at Such Times Sidney P Schwartz Jack Orloff and Charles Fox[8] (Montefiore Hosp New York City) made clinical electrocardiographic and phonocardiographic studies of cardiac arrhythmias preceding transient ventricular fibrillation in three patients with auriculoventricular dissociation Attacks of transient ventricular fibrillation in patients with complete heart block were invariably preceded by three abnormalities—lability of ventricular rate ventricular premature extrasystoles and fibrillary waves which invariably followed premature ventricular beats Fibrillary waves produced no acoustic vibrations detectable by phonocardiogram

Short runs of premature ventricular beats alternated haphazardly with isolated or short groups of fibrillary waves of the ventricles so as to increase in frequency and duration until the fibrillary process supervened and resulted in prolonged attack of syncope Marked depres

Temporary paresthesias of hands and feet were noted however

Reports of beneficial effects from calcium administration in potassium intoxication were verified in two patients Since relief from potassium intoxication with sodium chloride also has been reported the authors believe *that their usual practice of administering* infusions of glucose sodium chloride sodium bicarbonate and whole blood to patients in uremia may have effected improvement because of the sodium chloride effect on hyperpotassemia

Characteristic electrocardiographic changes *in* potassium intoxication are *(1)* high narrow T wave *(2)* broadened and perhaps slurred QRS interval (3) loss of P waves and (4) cardiac arrest with irregular undulating potentials of low voltage Correlation of specific electrocardiographic changes with specific serum potassium concentrations is impossible because these abnormalities are influenced by serum level of other electrolytes particularly calcium Exact significance and pathogenesis of electrocardiographic changes in hyperpotassemia have not been clarified

Pathogenesis of Left Bundle Branch Block was studied by Hakon Rasmussen and Torjus Moe[7] (Oslo) Since production of bundle branch block in dogs by section of branches of the bundle of His it is generally assumed that bundle branch block is always the result of damage to one of the branches of the bundle of His Recently similarity of electrocardiograms of left ventricular hypertrophy and of left bundle branch block has been emphasized

Previous investigations suggested that left bundle branch block might be the result of great enlargement of the left ventricle in absence of any local lesion of the bundle branch In the present study clinical x ray and autopsy records of 100 patients with permanent left bundle branch block were analyzed to determine validity of this hypothesis Diseases affecting the left ventricle

(7) Brit He rt J 10 141 147 J ly 1948

In subjects with heart failure T wave changes resembled those of normal patients in all respiratory phases in the recumbent position and in the standing position during normal respiration and normal inspiration In heart failure patients however T wave changes induced by inspiration in the standing position did not revert to normal on expiration as they did in controls In the 80 per cent of cardiac patients with upright T waves in ECG s taken under standard conditions T waves were isoelectric or slightly negative and S T segments were sometimes depressed in ECG s taken during expiration in the standing position In the other cardiac patients whose T waves and/or S T segments were abnormal in ECG s taken under standard conditions these abnormalities were accentuated during expiration in the standing position

Position changes had little effect on ECG s of dogs with normal hearts but in a dog in whom myocarditis had been induced by aconite injection ECG s were altered by change of position ECG s made with this dog in upright position showed widened QRS complexes and isoelectric T waves

Extracardiac factors consequent to position change were not believed to affect the ECG s Skin resistance did not change Diaphragm changes were not believed to alter ECG s significantly because during full expiration in the standing position the electrical axis is the same as during normal respiration in recumbency Likewise it is not probable that electrocardiographic changes resulted from changes in tone in the sympathetic nervous system

Leimdorfer proposes that T wave and/or S T segment changes produced during expiration in the standing position might be of value in detection of myocardial or coronary artery disease This test avoids the dangers inherent in the commonly used exercise test

Electrocardiographic Changes in Acute Gonococcic Arthritis and Myocarditis Simulating Acute Rheumatic Polyarthritis Edward Shapiro Maurice L Lipkis

sion of ventricular conduction before onset of ventricular fibrillation was suggested by alterations in cardiac rhythm during auriculoventricular dissociation and was confirmed by ECG s during a premonitory period which showed bizarre deformed ventricular complexes and prolonged RS T segments with progressively inverted T waves

Phonocardiograms indicated that deformed ventricular complexes resulted from superimposition of ventricular premature beats on one another Onset of periods of ventricular fibrillation was accompanied by periodic variability of sphygmic intervals between basic ventricular complexes and yielded irregular pulse pauses which could be recognized clinically Transient ventricular fibrillation in man has never been observed to start abruptly without such premonitory signs Clinical diagnosis of transient ventricular fibrillation may be suspected in patients with complete heart block by detection of electrocardiographic abnormalities in tracings made before development of syncopal attacks

Electrocardiographic Response to Changes of Posture during Respiratory Arrest Following Deep Inspiration or Expiration Clinical Significance Alfred Leimdorfer[9] (Illinois Neuropsychiatric Inst) made electrocardiograms on 65 healthy persons and 116 patients in heart failure both in recumbent and standing positions ECG s with the patient recumbent were made during (1) normal respiration (2) respiratory arrest after maximal inspiration and (3) respiratory arrest after maximal expiration preceded by maximal inspiration and were repeated in these three phases with the patient standing Patients again resumed the recumbent position and ECG s were obtained during normal respiration

In normal subjects in the recumbent position T waves varied in height in different phases of respiration but never became negative Standing position produced T waves often isoelectric or slightly negative on inspiration which became positive on expiration

(9) A n I t M d 9 1043 1055 Decembe 1948

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Electrocardiographic Changes in Acute Gonococcic

Julius Kahn and John B Heid[1] (Univ of Southern California) demonstrate an exception to the axiom that polyarthritis with electrocardiographic changes is pathognomonic of acute rheumatic fever Acute gonorrhea caused this syndrome in four cases reported by the authors

CASE 1 —Woman 22 had migratory polyarthritis fever leukocytosis and a rapid sedimentation rate An electrocardiogram showed changes in T waves Salicylates given for 49 days were without benefit and finally an x ray revealed septic arthritis Progression of arthritis and fever were halted in five days by administration of sulfathiazole and a diagnosis of gonococcic arthritis and myocarditis was made

CASE 2 —Girl 19 had migrating polyarthritis fever leukocytosis rapid sedimentation rate and prolonged P R interval and T wave changes characteristic of acute rheumatic fever Treatment for 57 days was without benefit An x ray revealed a septic joint and gonococci were found on urethral and cervical cultures Penicillin affected cure in seven days and a month later an ECG was normal

CASE 3 —Woman 21 with abnormalities similar to those in Case 2 failed to respond to salicylates given for one week Septic arthritis was demonstrated radiologically and positive complement fixation for gonorrhea was obtained Sulfadiazine arrested the arthritis and effected cure in two days An ECG was abnormal 17 days later and a permanently ankylosed ankle remained

CASE 4 —Girl 16 had migrating polyarthritis continuous fever leukocytosis rapid edimentation rate and vaginal discharge A diagnosis of gonorrheal arthritis was made and cure effected with penicillin in three days Complement fixation for gonorrhea was positive ECG s were characteristic of acute rheumatic fever

The electrocardiographic changes in these patients were probably caused by so called toxic myocarditis secondary to gonorrheal infection

Atrial Infarction with Diagnostic Electrocardiographic Findings Herman K Hellerstein (Chicago) reports a case of atrial infarction in a man 61 in whom the correct antemortem diagnosis was made on the basis of serial electrocardiograms showing changing auricular mechanisms with coarse auricular fibrillation vary

(1) Am J M Sc 217 300 307, M rch 1949
(2) Am He rt J 36 4 430 S pt mbe 1948

ing degrees of auriculoventricular block and elevation of the P T (P R) segment in leads II and III The patient was in shock when admitted to the hospital and died the sixth hospital day Autopsy revealed a recent infarct superimposed on an organizing infarct of the posterior wall of both atria Massive recent infarction was superimposed on an old infarct of the interventricular septum and posterior wall of the left ventricle with acute fibrinous pericarditis Thrombosis was found in the right main coronary artery and old arteriosclerotic occlusion of the left circumflex and left anterior descending rami

Hellerstein believes infarction of the atria to be more common than is generally recognized Necessity for recognizing this condition lies in the fact that it is often complicated by pulmonary embolism and by disturbances of conduction Arrhythmias such as auricular fibrillation auricular flutter and premature auricular beats may precipitate congestive failure if they are not controlled

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PERIPHERAL VASCULAR DISEASE

The following article illustrate the rapid advances being made both in diagnosis and in treatment of periph ral vascular d sease As yet there is no consen us concerning the relative value of vaso dilator substances such as tetraethylammonium salts niacin and histamin as compared with each other with physical methods and with urgical procedures —Ed

Studies on Pathogenesis of Arterial Disease Russell L Holman[3] (Louisiana State Univ) found that he could produce necrotizing arteritis at will by inducing kidney lesions in dogs on high fat diets Arterial lesions resulted if the diet was fed for two months or longer before kidney damage was produced The diet could be fed indefinitely at least as long as a year without causing blood vessel changes unle s kidneys were damaged Essentially it was low in protein and high in fat with 43 per cent of calories derived from

(3) S th M J 4 108 114 F bru ry 1949

fat 50 per cent from carbohydrate and only 7 per cent from protein. Lesions were induced by heavy metal injury, infection with Leptospira canicola or bilateral nephrectomy.

The earliest recognizable anatomic change was edema and swelling of collagen on both sides of the internal elastic membrane but usually more noticeable on the medial side. Collagenous fibers stained more intensely with eosin and frequently showed fragmentation. This was rapidly followed by exudation of polymorphonuclear neutrophils and fibrin which created a typical picture of intense necrotizing arteritis. If the animal lived long enough (this can be controlled by grading degree of renal insufficiency produced) healing occurred in the usual manner with scar formation.

These lesions were found in elastic arteries, muscular arteries and arterioles in almost every organ except kidney and liver. They were observed as early as four days after experimental induction of renal insufficiency. Analysis incriminates one or more lipid substances contained in but not unique to cod liver oil. Lesions were induced in 48 of 55 dogs whose diets contained cod liver oil and in 5 of 117 dogs whose diets did not contain it. The diet factor is heat stable, is not readily oxidized and is not vitamin A or D. Studies are being continued in an effort to define this factor. Despite all indirect evidence incriminating a lipid substance the author was unable to find direct evidence of fat metabolism disturbance. Lesions contained no material stainable with any fat staining dyes and estimation of the common fat fractions in the blood showed no abnormal concentrations.

Development of lesions could be prevented or decidedly retarded by concomitant feeding of vitamin E or cholesterol started up to three days after induction of renal insufficiency. Although some dogs had high blood pressure, hypertension was not an invariable precursor of arterial lesions.

Because of the fat antioxidant properties of vitamin E and because vitamin E prevents or del ... onment

of these lesions Holman has speculated that lesions result from tissue saturation of some fat fraction which the injured kidney is unable to metabolize normally

Office Diagnosis of Peripheral Vascular Insufficiency is discussed by Walter Redisch[4] (New York Univ) In the history of the patient with peripheral vascular disease sensitivity to heat or cold is of great importance Use of ergot lead arsenic epinephrine derivatives or pituitrin® should be recorded Certain occupations such as typing piano playing or use of pneumatic tools may be significant Tobacco is one of the greatest enemies and moderate use of alcohol one of the greatest aids to management of arterial disease Fleeting red streaks or minimal swelling of extremities suggest Buerger s disease Polycythemia or diabetes should be detected if present

Peripheral arteries should be palpated and varicosities searched for When a coil of veins is found it is palpated to detect thrill if thrill is present and the skin of the area warm diagnosis of arteriovenous fistula is reasonably certain Auscultation usually reveals a bruit Deep palpation may reveal cords of old thrombophlebitis Short superficial cords suggest superficial thrombophlebitis of Buerger s disease

The Landis Gibbon test is a more reliable means of determining degree of arterial spasm compared with degree of permanent occlusive change in an extremity than is use of small dermatherms with wide ranges of error In this test the lower extremities are exposed to room temperature for 30 minutes and then the upper extremities are immersed in water at 109 F for an hour in a room kept at 41 F The more the temperature and color of the legs improve the more spasm is being released

Tests of the venous system include Homans sign for detection of deep thrombophlebitis and many tests for determination of competency of the veins in varicositie In the former retroflexion elicits calf pain in presence of thrombophlebitis The oldest test for varicosities is

(4) J M Soc New J sey 46 4 9 J n ry 1949

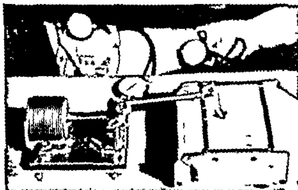
the Brodie Trendelenburg test in which the leg is elevated and the saphenous vein digitally occluded near the groin The patient then stands and digital pressure is released immediately The test is then repeated with pressure being maintained for 30 seconds and then released The slower the varices fill the more competent are the valves The first maneuver gives more information about competency of the saphenous and the second more about that of the communicating veins In the modified Perthes test a tourniquet is applied around the upper part of the thigh and the patient told to walk around briskly If varices disappear the saphenous veins are incompetent but communicating veins competent If varices become more prominent there is deep vein obstruction By repeating this test with tourniquet around the middle of the thigh and just below the knee incompetent communicating veins may be localized In a modification of this test an Ace bandage is applied from foot to groin and the bandage unwound until bulging vessels indicate the area of incompetent communicating vessels

Tonoscillography after Exercise New Method for Early Diagnosis of Organic Arterial Disease Leading to Intermittent Claudication and for Differential Diagnosis of Organic and Functional Arterial Diseases with Special Type of Apparatus With this method Borje Ejrup found improved pulsations and blood pressure in the extremities after exercise in normal persons but decreased pulsations and fall in blood pressure after exercise in patients with occlusive disease of the peripheral arteries

The apparatus used is shown in Figure 95 It consists of an automatic oscillographic blood pressure recorder adapted for registration of blood pressure and pulsation either with two separate cuffs or with one single cuff With the two cuff system the pressure remains at 50 mm Hg in the distal cuff and rises in the proximal cuff during recording Proximal and distal

(5) Act med Scand n v supp 211 1 130

cuffs register pressure and pulsations respectively With the one cuff system both pressure and pulsations are obtained from the same cuff With this system too registration takes place during the inflation phase Pulsations are transmitted in the form of variations in electric potential by means of a manometer These in turn are amplified to a magnitude strong enough to rotate a pen around a vertical cylinder Both cuffs re



F 95—T p w f app t h w g m l & ll w l i t p ll d w t g p n l P pe un ll f ly right At t p n b se ff ppl d bel w k nd d m ll f l g (C rt y f E) p R A c m d S nd n pp 211) 130 1948)

ceive air from gas containers The paper remains stationary during recording but moves 2 cm after each recording The amount of exercise is carefully standardized

With these tests it was found that the circumference of the calves was diminished after exercise in patients with typical claudication but was increased after exercise in normal persons Recordings made indicated that contraction occurred after exercise in arteries distal to the occlusion Ejrup believes that this vasoconstriction results secondarily from mechanical obliteration and the pumping mechanism of the muscles

The inverse recovery phase (duration of arterial contraction after exercise) was directly proportional to the

degree of total mechanical obstruction (damaged area plus collaterals) In all patients with definite peripheral organic changes the inverse recovery phase exceeded 1 minute and in many patients lasted as long as 15 20 minutes Certain tests indicated that vasoconstriction of the afferent arteries resulted from a general heightened vasoconstrictor tone added to the mechanical effect of organic obstruction In normal persons inverse reaction was sometimes seen in the first oscillogram made after exercise but it lasted only 45 seconds and was followed by a rise in pressure and improved pulsations The reaction was thought to depend on heightened vasoconstrictor tone

It is concluded that typical intermittent claudication is always attended by vasoconstriction but that it is probably secondary to a fall in blood pressure and is not due to any tendency to spasm Spasm could not be demonstrated in large arteries which were free of organic arterial changes Patients with anemia have not yet been examined but it is possible that inverse recovery might be somewhat prolonged in presence of anemia Since anemia is rare in patients with claudication it should not present any difficult diagnostic problem

In cases of typical claudication Ejrup found that one minute is sufficient as a limit for the inverse recovery phase from spasm or vasoconstriction Borderline cases should be investigated by arteriography

Arterial Embolism J R Learmonth[6] (Univ of Edinburgh) lists sources of emboli as left auricle in auricular fibrillation left ventricle after coronary occlusion atheromatous plaques in proximal segments of vessels thrombi in veins of patients with patent interatrial septa, vegetations in bacterial endocarditis and tumor cells From the surgical standpoint arterial emboli may be divided into those *involving the visceral and cerebral* arteries which are not amenable to surgery and those of the aorta and peripheral arteries which may be approached surgically

(6) Ed b gh M J 55 449 46 A gu t 1948

Immediate treatment of patients with emboli in the aorta or peripheral arteries should be directed to preservation of adequate blood volume maintenance of blood pressure and adequacy of collateral circulation After the embolus has lodged availability of collateral channels will depend on anatomic arrangement of vessels at the embolus site amount of arterial spasm in the major artery and collateral channels propagation of thrombosis from the point of embolism and amount of arteriosclerosis present

First aid treatment of patients includes immediate administration of 10 000 I U of heparin reduction of local catabolism by maintaining the threatened part at 15 20 C suppression of pain and induction of sleep to promote vasodilatation and avoidance of use of digitalis except in presence of cardiac failure

If aortic emboli must be removed Learmonth favors the transperitoneal route and use of anticoagulants for 7 10 days after operation

Clinical features of embolism in peripheral arteries are pallor of the limb absence of peripheral pulses paralysis anesthesia and sometimes pain Learmonth believes that patients with peripheral emboli seen within 10 hours of onset should be given heparin If heparin is to be of value unmistakable improvement should appear within two hours If no improvement is apparent embolectomy is indicated The ultimate result depends on the site of arterial obstruction

Plantar Fixation Sign Diagnostic Aid in Acute Arterial Interruption of Lower Extremity R Bernard Pomerantz[7] (San Antonio Tex) while examining men with vascular injuries in an evacuation hospital during World War II observed that complete interruption of the main stem artery of the lower extremity produced in as little as five hours a degree of muscle fibril swelling which although not appreciably increasing the diameter of the affected calf interfered with passive stretching of the muscles so as to render the foot incapable of dorsi

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flexion beyond a right angle When attempts were made to flex the foot passively as in eliciting Homans sign the foot could not be flexed beyond 90 degrees although unless there was some obvious cause of pain such as fracture of the ankle no pain was elicited The sensation produced by the profusely edematous muscle which had reached its maximal passive extension was quite different from that of a spastic muscle which still retained good tone The sensation resembled that to be expected if the foot were attached to a rope

Patients with complete interruption of a main stem artery of a lower extremity may be expected to have no peripheral pulsations in the extremity and to have the plantar fixation sign In addition however in some patients peripheral pulsations will not be felt for reasons other than complete interruption of a main stem artery In such persons absence of a plantar fixation sign may be of great clinical significance

Venous Thrombosis Alton Ochsner[8] (Tulane Univ) emphasizes the necessity of differentiating thrombophlebitis and phlebothrombosis Thrombophlebitis is characterized primarily by inflammation of the venous wall with secondary intravascular clots whereas phlebothrombosis is characterized primarily by an intravenous clot due to changes in blood coagulability or to venous stasis In phlebothrombosis the thrombus is not attached to the vein by inflammation and therefore can easily be dislodged with development of a pulmonary embolus In thrombophlebitis inflammation firmly binds the intravascular clot so that the danger of pulmonary embolism is slight Impulses originating in the involved vein are carried over the sympathetic nervous system to the ipsilateral arterioles and result in arteriolar spasm of the involved extremity with pronounced pain and pallor Phlebothrombosis occurs most frequently in the deep veins of the calf probably because stasis is maximal in this region Thrombophlebitis gives rise to severe clinical manifestations but phlebothrombosis is accom

(8) Su g ry 24 445 451 Septembe 1948

panied by few or no symptoms Elevation of pulse rate out of proportion to elevation of temperature suggests the presence of phlebothrombosis Often the pulse is raised in a stepladder manner In most instances the erythrocyte sedimentation rate is increased

Phlebothrombosis is usually diagnosed only by careful examination of the patient The calves and feet of all patients past 40 who have had any tissue injury or who are confined to bed should be examined Tenderness on compression of the calf or pain on forced dorsiflexion of the foot suggests the condition

Though the patient with thrombophlebitis has severe symptoms he is in relatively little danger He is likely however to have persistently disabling sequelae unless adequate therapy is instituted early By contrast the patient with phlebothrombosis is always in danger of massive and perhaps fatal pulmonary embolism

Phlebothrombosis may be prevented by avoiding tissue injury during surgery by active mobilization of the lower extremities by deep breathing and by application of compression bandages to the lower extremities to obliterate superficial veins and accelerate blood flow through the deep veins When phlebothrombosis occurs ligation should be performed immediately Under local analgesia a longitudinal incision is made over the femoral vein The artery is retracted and the vein exposed Ligatures are placed loosely around the profunda saphenous and femoral veins above and below the profunda but are not tied A transverse incision is made in the superficial femoral vein distal to the junction of the profunda femoris A glass suction tube is introduced proximally and gentle suction maintained until the clot proximal to the opening of the vein is removed The vein is then ligated above the opening The profunda femoris is seldom involved so usually only the superficial femoral vein is ligated and divided The procedure should be done bilaterally because of the high incidence of involvement of both legs in this condition

tion secured by anesthetization of the regional sympathetic ganglions with procaine hydrochloride With the patient in the lateral decubitus position spots two finger breadths lateral to the spinous processes of the first second third and fourth lumbar vertebrae are chosen cutaneous wheals are made at these points and a long fine lumbar puncture needle is introduced perpendicularly to the skin until it impinges against the transverse processes The direction of the needle is then changed slightly either above or below and the needle is introduced for an additional two fingerbreadths In this location 5 cc of 1 per cent procaine hydrochloride is injected so that the area in which the sympathetic nerves are located is flooded This procedure is repeated at each of four points and the whole procedure is repeated daily as long as the patient has fever Almost immediately after injection there is complete relief from pain

Visceral Thrombophlebitis Migrans Isadore E Gerber and Milton Mendlowitz[9] (Mount Sinai Hosp New York City) found autopsy reports on five patients with migrating visceral thrombophlebitis in the medical literature They reviewed these and six additional cases from their own hospital

This form of thrombophlebitis is distinct from other forms of vein inflammation It affects both peripheral and visceral veins haphazardly Degree duration and distribution of venous involvement are variable It is usual for short segments of medium and small sized vessels to be involved but in more severe cases long segments or complete venous systems may be thrombosed Veins of the lower extremity are affected more often than those of any other region but the most typical course is transitory involvement of vessels of both upper and lower extremities with occasional involvement of visceral veins Usually the course is benign and the disease subsides spontaneously in from a few weeks to months Recurrences may take place as long as years later Usually the affected veins are recanalized and ex

(9) Ann Int Med 30 560 579 March 1949

cept for minor sequelae such as postural edema there are no residua

It is not known whether this condition is primarily an inflammation of the vein wall with secondary thrombosis or primarily thrombosis with secondary involvement of the vein wall The inflammatory exudate is predominantly polynuclear in acute stages and lymphocytic and monocytic in later stages At times inflammation extends into the perivenous tissues

Congestion with or without hemorrhage is the rule and edema or serous effusion may occur in severe cases Infarction is rare and has been observed only in the intestines and in the adrenals In the bowel secondary ileus and arterial spasm may cause further obstruction of circulation and in the adrenal collateral circulation is very poor Practically every organ in the body may be affected The authors believe that lung involvement may be the result of pulmonary embolism from phlebothrombotic areas elsewhere Though the diagnosis of coronary occlusion from thrombophlebitis migrans has been made clinically it has not been proved at autopsy Liver involvement may result from extension of thrombophlebitis of the inferior vena cava or of the portal veins Involvement of the portal vein commonly results in ascites and the other sequelae of portal hypertension

Lesions of the splenic vein have occurred in association with mesenteric or portal thrombophlebitis The most common visceral vein involved in migratory thrombophlebitis is the mesenteric Symptoms are usually abdominal pain fever distention leukocytosis and at times prostration Many patients recover spontaneously but many die Thrombophlebitis of renal veins has been observed in a number of instances and in one patient gave rise to the full blown syndrome of lipoid nephrosis Thrombosis of the adrenal glands occurred in three of the authors six patients but has not previously been reported Terminal clinical findings in these patients were abdominal pain nausea sudden rise of temperature to 104 F confusion cyanosis and coma Involve

ment of the cerebral veins in this condition is not rare

Systemic manifestations of migrating thrombophlebitis include fever leukocytosis anemia and thrombocytopenic purpura Six fatal cases of thrombocytopenic purpura associated with thrombophlebitis have now been reported but the nature of the association between these two conditions is not known

Temporal Arteritis Review of Literature and Report of Five Additional Cases is presented by Roy C Crosby and Richard C Wadsworth[1] (Tufts College) Since the original description of temporal arteritis in 1932 43 cases have been reported but the fact that 7 cases are reported in each of two articles and 5 are reported in the present article indicates that the condition is not as uncommon as the rarity of reported cases suggests

Constancy of major clinical findings in patients with this condition is striking Local symptoms consist of severe throbbing headache with swollen tender nodular and thrombosed temporal arteries and pain in the scalp face jaws eyes and temporomandibular joints Systemic symptoms of fever malaise weakness anorexia and weight loss have been reported in almost all cases Characteristic changes in temporal arteries make diagnosis obvious and differential diagnosis presents no problem No organism has been found consistently but cultures of biopsy specimens of artery segments have not been taken in most instances There is no clinical evidence that allergy is a causative factor Since the disease has occurred in edentulous patients the possibility of oral sepsis being the etiologic factor seems remote Distant foci of infection have not been proved to cause the condition The fact that the disease occurs mostly in patients aged 55 79 suggests that a degenerative arterial disease is involved Because of the location of the temporal arteries trauma may be a factor

Evidence of arteritis of other branches of the external carotid artery has been stressed by some authors but study of the anatomic distribution of temporal ar

(1) Arch Int Med 81 431 464 Ap 1 1948

teries shows that this does not necessarily occur Pain over the face might result from involvement of the transverse facial branch of the temporal artery and difficulty in mastication and pain in jaws and temporo mandibular joints from involvement of branches of the temporal artery supplying the masseter muscle and tem poromandibular joints Pain and redness around the eyes and over forehead and scalp may be accounted for by involvement of anterior temporal branches Similar symptoms in parietal and occipital regions may be at tributed to lesions of posterior branches

Evidence of arteritis in vessels other than the tem poral artery is scarce Disease of retinal vessels is a common cause of transient amaurosis and results in blindness in a third of patients with temporal arteritis It has been concluded that blindness in this disease re sults from retinal or optic nerve ischemia from arteritis In autopsies of four patients similar vascular lesions were found in other vessels

Lesions of this disease are sufficiently uniform to sub stantiate the concept that this disease stands apart from other known vascular diseases The pathologic picture is that of a granulomatous reaction involving all coats of the artery but usually the media most severely Ac companying veins and nerves may be involved in the inflammatory process

Peripheral Vascular Disease in Lungs is discussed by Robert P Barden and David A Cooper (Univ of Penn sylvania) Conditions which may produce changes in the shadows of the peripheral vascular system in chest x rays include vascular congestion intrinsic obstruc tion of blood vessels intrinsic disease of blood vessel walls obliteration of vessels by adjacent pulmonary dis ease or hypersensitivity states and toxins causing in creased permeability Pulmonary vascular congestion may result from heart failure congenital heart disease or hemangiomas Intrinsic obstruction of blood vessels may result from thrombosis embolism trauma poly

( ) Am J R tg 1 61 17 2 J ry 1949

cythemia leukemia parasites or tumor emboli Intrinsic disease of blood vessel walls may be produced by sepsis syphilis arteriolar sclerosis rheumatic fever or scleroderma Pulmonary disease which may obliterate adjacent vessels include pneumonia tuberculosis silicosis carcinoma abscess and emphysema Hypersensitive states and toxins which cause increased permeability include periarteritis nodosum exfoliative dermatitis influenza lupus erythematosus glomerulonephritis eclampsia beriberi and sulfonamide poisoning

To illustrate these possibilities the authors report cases of pulmonary hemangiomas associated with subcutaneous hemangiomas myeloid leukemia with pulmonary infiltration carcinoma of bile ducts with pulmonary metastases rheumatic pneumonia and asthma attributed to periarteritis nodosa

Treatment of Deep Peripheral Thrombophlebitis by Paravertebral Sympathetic Block A M Boyd[3] (Univ of Manchester) believes that it is not sufficiently appreciated that acute thrombophlebitis responds dramatically to paravertebral sympathetic block This method was first suggested by Leriche and was subsequently popularized in America by Ochsner and DeBakey The technic is simple safe and within the scope of any practitioner with a suitable needle and procaine hydrochloride

The natural course of deep thrombophlebitis includes weeks of complete invalidism followed by months or years of severe disability usually ending in a heavy aching limb which becomes edematous after walking or standing

Though the cause of thrombophlebitis is unknown there are certain important predisposing factors These include slowing of the circulation particularly during bed rest and injury to the blood vessel intima from mechanical trauma as in tearing crushing or stretching of veins in contusions and on application of tourniquets Intimal damage may also be brought about by infection Increased blood coagulability is a further predis

(3) Cl J 77 84 89 M y Jun 1949

posing factor and may result from anemia or from ab sorption of products of tissue damage either traumatic as in operations or from neoplastic destruction

Intimal damage leads to formation of clots Irritation of the vessel wall produces peripheral spasm of both veins and arteries Spasm leads to anoxia and stasis and thereby facilitates extension of clotting The clot extends upward until it is stopped by the constricting action of tendons ligaments and fascial bands or the brisk flow of a large tributary There are two distinct types of deep thrombosis Iliofemoral thrombosis seldom occurs spon taneously or after mild trauma but nearly always with immobilization after operation or childbirth or as a com plication of typhoid fever or pneumonia It is most com mon in middle or late life After 24 hours of vague malaise with unexplained fever and tachycardia pain of variable severity may develop in the groin thigh knee or calf Edema of the legs is visible 12 24 hours after onset of pain The limb is pale cold and cyanotic and peripheral pulses are diminished Occasionally in less acute involvement the foot is warm There is tenderness along the course of the femoral vein and in the iliac fossa The acute phase may last 10 days to 6 weeks and is followed by a chronic phase in which the leg is cold cyanotic aching and edematous In the other type of thrombophlebitis the peripheral deep veins of the lower leg are involved The process begins most commonly in the veins of the soleus muscle but may start in any of the deep groups It occurs in the active phase of life and is nearly always associated with minor trauma such as sprains or strains In an acute attack severe pain in the calf of sudden onset may occur after some insignificant strain It may develop while a person is playing tennis or is walking Pain is variously described and is asso ciated with fever tenderness in the calf and malaise The calf will be warmer on the affected side and the foot cold and pale In less acute types there may be no his tory of trauma The first symptom is light pain in the calf on walking up stairs The leg is edematous cold

and cyanotic and pulses are diminished Slight tenderness is detectable on deep palpation of the calf and there is pain in the calf on dorsiflexion of the foot Swelling diminishes with bed rest but returns on resumption of activity

If the foot is pale and cold and arterial pulsations are diminished one may assume that there is sufficient vasospasm to warrant lumbar sympathetic block After this procedure is done cessation of pain can be expected

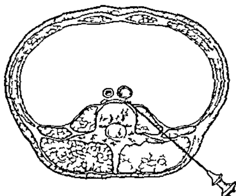


Fig 96 (Courtesy of Boyd A M Clin J 77 84 89 May June 1948)

within a few minutes and disappearance of edema in two or three days Temperature and pulse rate are usually normal 48 hours after injection The foot of the bed should be raised on blocks and the patient kept flat A second injection is sometimes required 24 hours later Response is much better in acute involvement

TECHNIC —The patient lies on the unaffected side with knees and thighs well flexed to straighten out the lumbar curve A pillow is placed under the loins to open out the space between the transverse processes A point is taken three fingerbreadths lateral to the second lumbar spine but the exact distance depends on the patient s size Unless he is unusually obese an ordinary 12 cm needle will do The needle is introduced at an angle of about 20 degrees from the horizontal plane (Fig 96) After the point strikes the transverse process it is directed above or below the process and advanced r two finger

breadths when it lies near the anterolateral aspect of the body of the vertebra After aspiration to verify that the point of the needle is not in a blood vessel 20 30 cc of 2 per cent procaine hydrochloride is injected It flows up and down the paravertebral gutter

Boyd does not believe it necessary to make separate injections at the level of the first to the fourth vertebra Undesirable sequelae are practically never seen though occasionally a branch of the lumbar plexus is struck while the needle is passing through the psoas muscle thus giving rise to sharp pain down the side

Syncardial Massage as Method for Improving Blood Circulation is advocated by Maurice Fuchs[5] (Bern) This involves a special apparatus which delivers rhythmic pressure impulses to the vessels of a designated portion of the extremities and functions as an auxiliary peripheral heart To be effective these pulsations must be delivered to the peripheral vessels at the right time namely when the pulse wave from the heart has caused vessel dilatation Pressure on the vessels should also be applied while the heart is in diastole that is after the T wave and before the following P wave These impulses strengthen arterial constriction and improve flow through the capillaries as well as improve venous reflux to the heart

Fuchs has invented a special apparatus (Syncardon) for this purpose with controllable rate and rhythm of pulsations and with timing regulated by R wave of the electrocardiogram taken simultaneously

Indications for this type of therapy include gangrene perforating ulcer intermittent claudication Buerger s disease dead finger Raynaud s syndrome edema crural ulcer and chilblain Contraindications are thrombophlebitis acute inflammatory conditions rapidly spreading gangrene and aortic insufficiency

Objective results of syncardial massage in patients include increase in skin temperature improvement in oscillation values from the vessels disappearance of cyanosis erythema and return of palpatory pulsation

and cyanotic and pulses are diminished Slight tenderness is detectable on deep palpation of the calf and there is pain in the calf on dorsiflexion of the foot Swelling diminishes with bed rest but returns on resumption of activity

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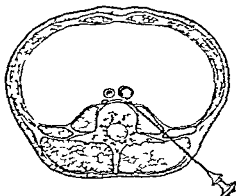


Fig 96 (Courtesy of Boyd, A. M Clin J 77 84 89 May June, 1948.)

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Raynaud s disease or dead fingers all reported signs of improved circulation They experienced greater warmth less pain and less stiffness in addition the skin was less cyanotic and swollen and its temperature was elevated The effect was usually noticeable 30 45 minutes after the ointment was rubbed in Application was usually made three times daily the effect lasting two or three hours Effects were somewhat less pronounced in patients who had not had sympathectomy Of the sympathectomized patients treated five had almost complete relief and six others definite improvement

Tetraethylammonium Chloride in Peripheral Vascular Diseases and Allied Conditions Its Uses and Limitations are outlined by Martin M Fisher[7] (New York City) In 1946 a method of blocking the autonomic ganglions by parenteral injection of tetra ammonium ion was reported In the form of tetraethylammonium chloride (TEAC) this substance was used instead of paravertebral sympathetic ganglion blocks caudal anesthesia spinal anesthesia and local nerve blocks to relieve vasospasm

Fisher recommends the following technic of injection after trial by more than 1 500 injections

TECHNIC—The maximal dose given is 5 cc The higher the blood pre sure the smaller the first dose Patients with blood pressures higher than 200 systolic are given 0 5 cc initially with pres ures between 172 and 200 1 cc between 162 and 170 2 cc between 142 and 160 2 3 cc and between 90 and 140 3 4 cc Because of development of some degree of tolerance subsequent injections must contain larger doses The patient is put in bed and instructed to lie flat for 45 minutes after injection The blood pressure cuff is placed on the arm above the injection site and blood pressure readings are taken repeatedly until three consecutive readings are stable With a no 25 5/8 in subcutaneous needle and a 5 cc syringe intravenous injection is made at the rate of 1 cc in the first 30 seconds and 1 cc/minute thereafter Injection is stopped when the size of the pulse in the other wrist diminishes Then blood pressure readings are taken repeatedly until pre sure rises again usually a matter of several minutes

The patient has a sense of warmth and paresthesia As blood

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of the foot vessels Pulse wave velocity is slowed The affected limb becomes functionally improved and edema of various origins disappears Hyperhidrosis and blood sugar are diminished Healing of severe trophic ulceration and gangrene is remarkable

Subjectively patients report diminution of pain paresthesias and itching They are able to tolerate greater changes in external temperature and the treated portion of the body feels warmer

Percutaneous Nitroglycerin Treatment in Cases of Peripheral Circulatory Disorders, Especially Raynaud's Disease Since 1944 Fredrik Lund[6] (Stockholm) has used nitroglycerin ointment to lower blood pressure to dilate coronary vessels and as local treatment for peripheral circulatory disorders By this method a high nitroglycerin concentration is achieved in the area of application where one hopes to cause vasodilatation

Ointments containing nitroglycerin in concentrations of 0 5-4 per cent have been used Most patients tolerated 1 Gm of 1 per cent ointment or 0 5 Gm of 2 per cent ointment rubbed into the intact skin without any resultant headache the commonest secondary effect Resorption was poor in areas where circulation was poor or where the skin was very thick It was influenced also by presence of sebaceous or sweat glands and by the consistency of the ointment base

About 30 arteriosclerotic patients with pregangrene or decubitus ulcers were treated Most of them experienced an increased feeling of warmth diminution of pain improvement in tissue consistency shedding of gangrenous tissue and healing of ulcerations An occasional patient found the ointment irritating and painful

Of 13 patients with intermittent claudication only 3 improved after use of the ointment Since pain in these patients resulted from muscle ischemia there was no reason to expect noteworthy results from treatment

Three patients with chronic frostbite or chilblain improved decidedly after beginning treatment Of 17 with

(6) A ta m d S a d n (pp 206) 130 196 1948

shock or as routine treatment for uncomplicated hyper tension

Method of Treatment of Obliterating Endarteritis with Trophic Lesions, in Extremities Eutrophic Effect of Niacin Derivatives While investigating different vasodilating substances for use in patients with peripheral vascular disease Bohumil Prusik[8] (Prague Czechoslovakia) found a 3 per cent solution of triethanolamine of niacin the most successful Injection of this substance causes a sudden sensation of heat in the head neck chest upper extremities and after a short time in the abdomen and lower extremities There is deep flushing of the skin of all parts but mostly of the head neck and upper half of the body During this period skin temperature increases 2 3 degrees C The reaction lasts 20 30 minutes and disappears gradually During this time the patient may have moderate abdominal pain Blood levels of niacin usually remain elevated about 6 hours and 24 hours after injection only about 2 5 per cent of the injected substance has been eliminated

Toxicity of 3 per cent triethanolamine of niacin is low no untoward reactions being detected when doses of 20 30 cc were injected daily for several weeks The maximal dose was 55 9 Gm in 40 days and the patient receiving it had no serious untoward reaction During treatment it is usually necessary to increase dosage The highest daily dose used by Prusik was 19 mg /kg body weight No abnormalities were produced in heart or kidneys by use of the substance and it was thought that vasodilatation took place not only in the extremities but also in the internal organs

Activity of this substance was counteracted by histidine and the substance was antagonistic to sulfonamides and penicillin Good results were achieved in all but 7 of 214 patients with thromboangiitis obliterans all but 3 of 312 with arteriosclerosis obliterans all but 11 of 45 with diabetic obliterating endarteritis all but 6 of 86 patients with acrocyanosis and all of 29 patients

(8) C d log 14 8 93 1949

pressure drops he has a sense of fatigue and notices that the heart rate increases The patient hould lie flat for 45 minutes because of postural hypotension and should be instructed not to drive a car home because of the possibility of pupillary dilatation

Among Fisher s patients best results were achieved in the 52 with acute thrombophlebitis All had some relief of pain 7 10 minutes after injection in half of the patients one injection was sufficient to relieve pain permanently No patient had a pulmonary infarct after injection

Among 13 patients with sudden acute arterial occlusion complicating auricular fibrillation only 1 improved after use of TEAC but none of the other patients was relieved by subsequent paravertebral block

As a diagnostic aid in selecting patients with essential hypertension for sympathectomy TEAC blocks produced significant drops in blood pressure comparable to those produced by sodium amytal* and in some instances even greater In 12 patients with thromboangiitis obliterans and in 404 with peripheral arteriosclerosis results were not encouraging but relief from pain was sometimes greater with TEAC than with morphine demerol* and papaverine

Dramatic relief was occasionally accomplished in acute hypertensive crises with hypertensive encephalopathy As a diagnostic aid in selecting patients with peripheral vascular disease for sympathectomy the drug was of particular value It was of value in relieving pain of causalgia Use of the drug in Meniere s disease and multiple sclerosis has been insufficient to warrant conclusions

There were no toxic effects from the 1 500 injections given Studies of gastrointestinal function and kidney function revealed no serious sequelae Fisher prefers use of TEAC to paravertebral block because it is more comfortable for the patient easier for the doctor less dangerous if the upper extremity is involved and can be repeated frequently Age is no contraindication to use of the drug but it should not be use presence [illegible]

upper half of the body became erythematous and the leg only mottled or even cyanotic This observation suggests the futility of giving vasodilators intravenously

Treatments were given weekly until exercise tolerance was increased to 10 blocks Then one treatment a month was given until tolerance of 18 20 blocks was attained when treatment ceased Number of treatments necessary for great improvement varied from two to five

Oscillometric readings before treatment were recorded for 11 patients and were invariably low Skin temperature of legs reported for two patients before and during treatment increased in both during treatment Radio sodium diffusion studies were conducted in the five cases reported Radioactive sodium was injected into an arm vein and a Geiger counter placed on the foot These studies were interpreted as indicating that treatment had effected an increase in diffusion rate of radiosodium into the lower extremities

Mufson emphasizes the effect of smoking pain and fear on accentuation of vasospasm

Treatment of Thromboangiitis Obliterans Two Year Follow Up after Sympathectomy is reported by William J Messinger Edmund N Goodman (New York City) and James C White[1] (Boston) Results of sympathectomy in thromboangiitis obliterans are so impressive that the operation is recommended for all patients with this disease in whom high vasoconstrictor tone can be demonstrated In evaluating results in 19 patients two years after operation it was found that 9 were asymptomatic and that 7 obtained partial relief All patients were men under age 45 with one exception a man aged 54 In 14 patients sympathectomie were restricted to lumbar ganglions in 4 both lumbar and thoracic (second third and sometimes fourth thoracic) ganglions were removed and in 1 patient only thoracic ganglions When thoracic ganglions were removed rhizotomy of the second intercostal nerve was done in addition Site of operation was determined by location of symptoms and signs

[1] J M d 6 1 8-1 6 February 1949

with Raynaud s disease Good results were achieved in only two of eight patients with syphilitic endarteritis

The most effective treatment was intravenous injection of 3 per cent triethanolamine of niacin in amounts of 5 cc the first day 10 cc the second day and if there were *no untoward reactions 20 cc the third day* and every day thereafter until improvement occurred The average course consisted of approximately 20 injections but as many as 40 were given to some patients Often injections were given in the posterior tibial artery at the inner aspect of the foot or in the popliteal fossa sometimes using local anesthetics In addition ulcers were treated by the usual methods Use of this drug enabled Prusik to limit to a great extent the indications for surgery especially amputation of the leg in patients with peripheral vascular disease

New Treatment for Relief of Obliterative Diseases of Peripheral Arteries Isidor Mufson[9] (Columbia Univ) reports that among 16 patients unable to walk more than 4 blocks without intermittent claudication exercise tolerance was raised to 12 18 blocks in 7 by histamine infusion into the femoral artery Night pain was eliminated in all

TECHNIC —Histamine acid phosphate 1 38 2 75 mg in 500 cc normal saline was introduced into the femoral artery through a 2 in 20 gauge needle at a rate of between 2 and 5 drops/heart beat Pressure in the bottle was elevated above diastolic blood pressure by attaching tubing of the manometer of a blood pressure apparatus to a glass tube inserted through the bottle stopper above the level of histamine solution The arm cuff was rolled up snugly and held with a stout elastic band The bottle stopper was held in place with strips of adhesive tape

Erythema spread over the lower extremity as histamine entered the femoral artery White areas suggested location and degree of block of larger vessels Such areas later became erythematous when collaterals were dilated by histamine When histamine was given rapidly enough to permit its escape into general circulation the

(9) A I t M d 29 903 913 N mber

monary embolus 12 days postoperatively None of the other patients given dicumarol® had thromboembolic complications Nineteen patients had hyperprothrombinemia the third postoperative day but clinical evidence of thrombosis did not develop Unexplained tachycardia and fever developed in 10 of this group during the post operative period

The authors conclude that all patients showing hyperprothrombinemia the second or third postoperative day should receive dicumarol® prophylaxis unless there are definite contraindications It is not necessary to reduce prothrombin concentration to dangerously low levels when dicumarol® is being used prophylactically Hyperprothrombinemia might be considered an indication for ligation by advocates of this method of therapy Hyperprothrombinemia occurs before thrombosis can be diagnosed by clinical examination When thrombosis is established prothrombin activity may be normal or even subnormal

Use of Anticoagulants in Treatment of Diseases of Heart and Blood Vessels is reviewed by Irving S Wright[8] (New York City) With prophylactic use of dicumarol® at Mayo Clinic in 832 patients after hysterectomy only 3 instances of venous thrombosis occurred as against the 33 which could be anticipated with conventional therapy Pulmonary embolism was not diagnosed in any patient and it was estimated that six such emboli would have occurred without treatment Among 500 general surgical patients at Massachusetts General Hospital given dicumarol® prophylactically none had fatal pulmonary emboli and it was estimated that 6 would have had fatal pulmonary emboli without treatment Results of treatment of coronary thrombosis with dicumarol® indicate that death rate can be reduced one third and incidence of thromboembolic complications reduced one half by use of anticoagulants [Details are reported in this YEAR BOOK page 623 —Ed]

Although some failures occur despite apparently ade

(8) A I t M d 30 30 91 J ry 1949

Review of sexual disturbances resulting from lumbar sympathectomy in over 100 patients showed that failure of erection and/or loss of ejaculation never occurred when the operation was unilateral and practically always occurred when it was bilateral Though the first lumbar root was most commonly incriminated no single lumbar ganglion was found to control sexual function in all patients

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ANTICOAGULANTS

The place of anticoagulant therapy in prevention of thromboembolic disease after operation after coronary occlusion and during congestive heart failure now seems to be established Evidence concerning the therapeutic value of these agents as compared to venous ligation after an initial episode of pulmonary infarction is not conclusive More studies are needed concerning the value and safety of long term anticoagulant therapy in ambulatory patients before this plan of management can be recommended—Ed

Prothrombin Activity Diagnostic Test for Early Postoperative Venous Thrombosis According to Rachel S Sandrock and Earle B Mahoney[2] (Univ of Rochester) definite increase in prothrombin activity of whole plasma the second or third postoperative day appears to be a warning of impending venous thrombosis Using a method similar to that described by Quick they studied postoperative prothrombin activity of 382 surgical patients of many types Thrombosis did not develop in any patient studied the first second or third post operative days who had not had preceding hyperprothrombinemia

Neither postoperative hyperprothrombinemia nor thromboembolic complications developed in 306 patients Thrombosis developed in 16 Dicumarol® was administered prophylactically to 41 patients being started in 18 immediately after operation and in 23 the third post operative day because of sudden rise in whole plasma prothrombin activity that day Because of inadequate dicumarol® therapy one patient had a nonfatal pul

(2) A n S rg 128 521 532 Septemb r 1948

was contraindicated or in whom operations were rarely followed by thrombosis favorable results of dicumarin prophylaxis became statistically significant This group clearly showed a lowered incidence of thrombosis Furthermore frequency of thrombosis was the same among men who received dicumarin as it was among those on early ambulation alone Women given dicumarin had a lower incidence of thrombosis than those on early ambulation Fatal pulmonary embolism did not occur among those receiving the drug but did occur in four patients on early ambulation

Early ambulation is seldom used alone in treatment of manifest thrombosis and cannot be properly evaluated The literature reveals that both heparin and dicumarin have been of great value in thrombosis and in prevention of fatal pulmonary embolism

Strombeck recommends early ambulation as the fundamental and most important measure in prevention of thrombosis It should be started the first day or at latest two or three days after operation It should be supplemented especially in women by dicumarin prophylaxis the day after operation and continued until the patient is fully mobilized Prothrombin percentage should be maintained between 10 and 30 (prothrombin index 40 60) Dicumarin is contraindicated in cases of liver injury special tendency toward hemorrhage incomplete control of bleeding from the wound and certain renal diseases Physicians and nurses should be trained to recognize early signs and symptoms of thrombosis so that combined heparin and dicumarin therapy may be started as soon as possible According to Allen early thrombosis must be stopped within 24 hours if risk of embolism is to be avoided Since anticoagulant influence of dicumarin is slow to take effect heparin must be used as a supplement during this period

Medical Aspects of Thrombophlebitis In the opinion of Edgar V Allen[4] (Mayo Clinic) clinical differentiation of phlebothrombosis thrombophlebitis and venous

(4) B ll N w York A d M d 4 491 504 A gu t 1948

quate therapy most therapeutic failures are attributable to inadequate anticoagulant therapy and occur when a minimal prothrombin time of 30 seconds is not maintained Some patients who had thromboembolic episodes despite apparently adequate doses of anticoagulants had malignant neoplasms of liver pancreas or elsewhere others had phlebitis migrans

Hemorrhagic complications occur in patients not given anticoagulants but are more frequent in those given them Serious hemorrhages in most instances resulted from use of poor prothrombin tests from careless supervision by the physician which led to overdosage from recent surgery or injury or from presence of conditions which contraindicate use of anticoagulants—blood dyscrasias serious liver or kidney disease or ulceration of any part of the intestinal tract

A small number of patients were given prolonged anticoagulant therapy in the out clinic in an attempt to prevent embolism from fibrillating rheumatic hearts Some success was achieved but therapeutic details were not entirely worked out It was not decided if quinidine should be administered to patients of this type

Neither heparin nor dicumarol® is an ideal anticoagulant New improved anticoagulants should be searched for

Attempt to Evaluate Different Modern Methods for Prevention and Treatment of Thromboembolism J P Strombeck[3] (Lund Sweden) evaluates early ambulation and anticoagulants in prevention and treatment of thrombosis and embolism and outlines a plan of treatment for these conditions A fundamental factor in development of venous thrombosis is retardation of venous return from the thrombosed area

Among 940 patients given dicumarin prophylactically 29 (3 1 ± 0 57 per cent) developed thrombosis Early ambulation was prescribed for 891 patients 50 (5 6 ± 0 76 per cent) developed thrombosis When figures were adjusted to account for those in whom the drug

(3) Act ch S in 97 113 134 1948

drug 3 4 per cent had minor hemorrhage and 1 8 per cent serious bleeding For control of such bleeding 60 mg synthetic vitamin K (menadione bisulfite) is administered intravenously and transfusion of fresh blood given to restore the blood lost Injection of vitamin K can be repeated at two hour intervals once or twice as needed

Dicumarol® is contraindicated in renal insufficiency after operations on brain or cord and in blood dyscrasias ulcerative lesions nutritional deficiency or hepatic disease associated with potential or actual prothrombin deficiency Allen believes anticoagulants to be valueless in treatment of subacute bacterial endocarditis

Among 1 513 patients given anticoagulants postoperatively 85 survived who would have been expected to die from pulmonary embolism and 250 were spared venous thrombosis or nonfatal pulmonary embolism Of 506 additional postoperative patients given dicumarol® prophylactically venous thrombosis occurred in only 2 and none had pulmonary embolus Consideration of the 288 medical patients given anticoagulants indicated that fatal pulmonary embolism was prevented by this treatment Nonfatal pulmonary embolism and venous thrombosis were rare

Anticoagulant therapy is usually continued for about 10 days in thrombophlebitis of the deep veins It is difficult to decide how soon patients should become ambulatory but it is probably wise to allow the patient up when edema has disappeared When he becomes active it is best to bandage the leg from the knee down with a rubber bandage 3 in wide and 15 ft long Bandage is applied in the morning over a lisle stocking and worn all day Once every month the bandage is discarded and if edema occurs the bandage is worn another month Many patients discard the bandage permanently within three to six months

Effect of Dicumarol® on Heart in Experimental Acute Coronary Occlusion Increasing use of dicumarol® to prevent thromboembolic phenomena and propagation of the thrombus after coronary thrombosis suggested to

thrombosis is ordinarily impossible He therefore considers the terms synonymous and for clarity uses thrombophlebitis to include all of them When there is only slight tenderness to pressure over the calf muscles or on dorsiflexion of the ankle it may be difficult to decide whether thrombophlebitis is present Phlebography has been of little help It is usually necessary to assume that the patient has thrombophlebitis

In determining the cause of superficial thrombophlebitis the physician should consider the possibility of trauma injection varicosity thromboangiitis obliterans polycythemia vera malignancy (especially of the bronchus stomach or pancreas) and lymphoblastoma Deep thrombophlebitis is most commonly caused by operation delivery and bed rest

Pulmonary embolism from superficial thrombophlebitis is rare but if thrombosis progresses close to the junction of the greater or lesser saphenous systems with the femoral or popliteal veins progress must be halted because from these locations emboli may be detached and pulmonary infarction result

Allen believes that anticoagulants for patients with thrombophlebitis do as much as or more than ligation of veins and he prefers anticoagulants to ligation in all cases except when anticoagulants are contraindicated No perfect anticoagulant is available Dicumarol® becomes effective a day or two after it is administered its effect persists several days after the drug is discontinued and its use requires the services of a skilled laboratory Heparin acts quickly and does not necessitate laboratory control but is expensive Heparin should be used when anticoagulant effect is needed quickly and dicumarol® when prolonged effect is necessary Dicumarol® is given in a dose of 300 mg the first day and 200 mg the second and each subsequent day when prothrombin is over 20 per cent On any day when the value for prothrombin is under 20 per cent dicumarol® is withheld

The sole danger associated with use of dicumarol® is hemorrhage Of 1 983 postoperative pat ts given the

the tie above the point of occlusion No mural thrombi were found in auricles or ventricles in either group of dogs Development of collateral anastomotic channels between the coronary arteries was the same in both groups

The authors conclude that dicumarol* produces no adverse effects on the myocardium of dogs which retard healing or development of collateral circulation in experimentally produced myocardial infarction

Anticoagulant Therapy of Coronary Thrombosis with Myocardial Infarction In 1946 the American Heart Association initiated a study of use of dicumarol* in myocardial infarction in 16 large hospitals Detailed records have been collected on 1 000 patients An analysis of the first 800 is reported by Irving S Wright Charles D Marple and Dorothy Fahs Beck[6] (New York City)

TECHNIC—Use of heparin during the first 48 hours was optional Dicumarol* was administered only after prothrombin determination Then 200 300 mg daily was administered until prothrombin time was 30 seconds and thereafter 50 100 mg doses were given daily when prothrombin time was between 30 and 35 seconds When prothrombin time was above 35 seconds the drug was withheld until it was again 30 seconds or less Prothrombin time was determined by Link Shapiro technic with undiluted whole plasma or by the Quick method Therapy was usually continued at least 30 days and preferably 30 days after the last thromboembolic episode Hemorrhagic manifestations were treated with synthetic vitamin K 60 70 mg and whole blood transfusion

Every effort was made to be sure that patients in treated and control groups were similar Of the controls 12 per cent received anticoagulant therapy usually for short periods after thromboembolic complications

Among controls 24 per cent died and among treated patients 15 per cent died Ten per cent of controls died of thromboembolic complications as against 3 per cent of those treated Death not preceded by clinically recognized thromboembolic complications occurred in approximately 14 per cent of controls and 12 per cent of treated patients Anticoagulants apparently lowered death rate

(6) J A M A 138 1074 10 9 Dec 11 1948

H L Blumgart A S Freedberg P M Zoll H D Lewis and S Wessler[5] (Boston) the desirability of learning whether adverse myocardial changes might result from this therapy It seemed possible for instance that the miliary myocardial hemorrhages commonly seen within infarcted areas could under dicumarol® result in progressive hemorrhagic extravasations or that other untoward effects might offset some of the possibly favorable effects of this drug

Accordingly in 31 dogs the left anterior descending coronary artery or in one instance a major branch was ligated Effect of oral administration of dicumarol® on the myocardium and coronary arteries was studied in 14 animals Three dogs were given heparin several hours postoperatively until the effect of dicumarol® was apparent Aim of dicumarol® therapy was to keep prothrombin time between 20 and 30 seconds or 20 12 per cent of normal prothrombin activity in dogs Fifteen dogs served as controls Animals were killed at various intervals after operation

Incidence and magnitude of hemorrhagic extravasations on the endocardium and pericardium were the same in treated and untreated dogs as were incidence and magnitude of miliary hemorrhages on microscopic examination of heart muscle In a small group of dogs given sufficient dicumarol® to elevate prothrombin time to levels as high as 132 seconds no increase in hemorrhagic phenomena was observed in the myocardium Size of infarcts in dicumarol® treated and untreated animals were similar Size of the infarcts was that anticipated on the basis of the artery occluded There were no apparent differences in healing or reparative processes in the hearts of treated and control animals Thrombotic occlusions of smaller arteries were found within the infarcted area in dogs receiving dicumarol® about as often as in the untreated group No thrombi were found in the region of the tie below the point of occlusion In one untreated animal a thrombus was found in the region of

(5) Am H t J 36 13 27 J ly 1948

bolism An average dose of 78 mg dicumarol® daily kept prothrombin concentration between 10 and 30 per cent Effectiveness of this low dosage was thought to result from the impairment of liver function usual in heart failure Administration of vitamin K was rarely neces sary and no hemorrhagic complications occurred

Incidence of pulmonary embolism was determined only after careful scrutiny of signs and symptoms usually thought to suggest embolism Elevation of temperature pulse rate or sedimentation rate was not considered suf ficient evidence for diagnosis of pulmonary infarction unless a pulmonary lesion could be visualized by x ray or the serum bilirubin or urine urobilinogen level was ele vated In the two patients in whom pulmonary embolism developed during treatment with dicumarol® there was evidence that dicumarol® effect was inadequate at the time embolism occurred

Case of Rheumatic Heart Disease with Periodic Ar terial Embolism Ambulatory Treatment with Dicu marol® is described by Howard B Sprague and Robert P Jacobsen[8] (Massachusetts Gen l Hosp)

Man 38 had been known to have rheumatic heart disease since 1930 although there was no history of rheumatic infec tion In 1934 he had an embolus to the spleen and later had five further episodes of embolism the last in 1947 necessi tating removal of the embolus from the left femoral artery

Auricular fibrillation was thought to have been pre ent 15 years Auscultatory findings were those of mitral regurgita tion and stenosis and the electrocardiogram revealed auricular flutter with varying block flutter rate being 480 and ventricu lar rate averaging 80 Embolism had recurred at roughly two year intervals during 12 years

After embolectomy in 1947 heparin was given Thereafter for 15 months (until time of writing) dicumarol® was given During administration of anticoagulants no further embolic phenomena were detected After the daily dose was standard ized at 50 mg prothrombin determinations were not usually necessary oftener than once a month Prothrombin time of 50 60 seconds was well tolerated Slight nasal bleeding occurred once when prothrombin time was nearly 80 seconds It was necessary to reduce weekly dosage of dicumarol® during the

(8) M Cl n N th Am 91 1309 1313 S pt mbe 1948

largely by reducing incidence of thromboembolic com plications

Although death rates were highest during the first two weeks they remained significantly high during the third and fourth week Therefore anticoagulant therapy should be continued approximately one month If not used before it may be begun as late as the second or third week or later if complications develop Greatest benefits in mortality reduction occurred in patients over 60 Treated patients had slightly more than one third as many thromboembolic complications as did controls

It is of interest that hemorrhagic manifestations oc curred in 6 per cent of controls They occurred in slightly over 12 per cent of treated patients and only half of these were severe

The authors conclude that anticoagulant therapy should be used in all cases of coronary thrombosis with myocardial infarction unless definite contraindication exists In absence of hemorrhagic conditions hemor rhage hazards are not sufficient to contraindicate use of anticoagulants provided there are facilities for adequate laboratory and clinical control

Dicumarol® Therapy in Congestive Heart Failure J H Wishart and Carleton B Chapman[7] (Univ of Min nesota) administered dicumarol® to 61 patients in heart failure in an effort to decrease incidence of embolic phenomena Incidence of embolic phenomena during dicumarol® therapy was 6 5 per cent and only one death was conceivably attributable to embolism Since minimal incidence of embolic phenomena previously reported among patients in heart failure has been 22 per cent dicumarol® during decompensation apparently provides valuable protection against thrombosis

All patients studied had unequivocal signs of heart failure Included were patients with myocardial infarc tion auricular fibrillation and mitral stenosis all of which independent of cardiac decompensation might be considered contributing causes to thrombosis and em

(7) N w Engl d J M d. 239 701 704 N v

prothrombin times were above 30 seconds and no deaths occurred No serious hemorrhages resulted and most patients were able to lead fairly normal lives and when necessary to support themselves and their families

Control of Dicumarol® Therapy John H Olwin[1] (Presbyterian Hosp Chicago) treated 99 patients actively or prophylactically with dicumarol® 50 as out patients Prothrombin determinations were made weekly on most of the outpatients Treatment of outpatients was continued for periods up to 23 months Some of them were out of the city for weeks at a time but sent blood samples to the laboratory for control

Bleeding occurred in 15 of the 99 patients In 13 of the 15 prothrombin level was between 1 and 11 per cent when bleeding became apparent and stopped when the level rose to between 15 and 20 per cent In the other two patients bleeding followed trauma when the level was 36 per cent The urinary tract was the most common site of bleeding

The author attributes his success with dicumarol® to the accuracy of the two stage prothrombin determination described by Warner Brinkhous and Smith which he used In this test clotting time is determined in the two stages in which blood normally clots This technic eliminates certain possibilities of error inherent in the Quick one stage prothrombin time determination used generally It also eliminates the possibility of variation of prothrombin time resulting from an abnormality in conversion rate of prothrombin in patients with an abnormal amount of prothrombin accelerator In addition it eliminates the possibility of error which might result from fibrinogen deficiency By providing for high neutralization of plasma it neutralizes the anti thrombin factor

In patients in whom bleeding developed withdrawal of the drug for one or sometimes two days was usually sufficient to bring the prothrombin level to within safe limits Since dicumarol® therapy was accurately con

(1) Am J M Sc. 17 4 7 437 Ap 1 1949

winter from 350 to 200 or 300 mg because of the tendency for prothrombin time to rise during respiratory infections In *one of these infections prothrombin time rose to 100 econd* and dicumarol® was omitted for two days *Prothrombin time then fell to 40 seconds* and the usual dosage was *resumed*

Although this was an uncontrolled experiment and the effectiveness of therapy in preventing embolism is un proved it illustrates the practicality *of giving* dicumarol® daily to a young ambulatory patient with mitral *stenosis* and multiple recurrert arterial embolism

Long Term Anticoagulant Therapy for Cardiovascular Diseases Prolonged anticoagulant therapy has *been sug* gested for treatment of certain patients with recurring thrombotic and embolic tendencies William T Foley and Irving S Wright[9] (Cornell Univ) treated 19 such patients for 5 20 months (*average 11 months*) with dicu marol ® Prothrombin time was checked every 7 14 days after careful standardization at more frequent intervals during several weeks or months of hospitalization Of *these 19 patients* 4 had *rheumatic heart* disease with auricular fibrillation 3 phlebitis migrans 7 *recurrent* phlebitis and 5 recurrent myocardial infarction Average weekly dose varied from 175 to 800 mg between 300 and 500 mg being given to 15 patients

Vigilance by the physician and co operation from the patient were necessary No effort was made to evaluate statistically results of therapy in this report Neither age *nor weight* was a determining factor *in* dosage require ments *Adequate protein intake helped stabilize require* ments in some patients and excessive alcholic intake sometimes affected requirements

An attempt was made to keep prothrombin times be low *60 seconds but prothrombin times of over 300 sec onds* occurred without serious hemorrhage *Invariably* excessive prothrombin times were controlled with vita min K and transfusions of fresh blood

No discernible liver or kidney damage occurred in any patient *There were no thromboembolic episodes while*

(9) Am J M S 217 136 14 F b r ~ 1949

four days and after a short intermediary period deter mination of the maintenance dose (300 450 mg) Pro thrombin time must be verified daily during the first week once it is stabilized around 20 per cent and main tenance treatment is instituted one or two control de terminations weekly suffice If prothrombin rate can not be determined regularly for any reason the so called safety treatment is resorted to 3 tablets the first day 2 or 3 the second 2 the third 1 or 2 the fourth 1 the fifth and then 1 every 24 hours prothrombin rate being verified once a week if possible This treatment is harm less if the patient is in good general condition and it may be used as prophylaxis It is important to distribute the medication evenly over the 24 hours for instance in the radical treatment 300 mg is given every 6 hours Della Santa observed seven mild hemorrhagic complica tions and three severe hematurias one of which was fatal these complications confirm the great fragility of old and arteriosclerotic patients in unsatisfactory nutri tional condition they respond rapidly to transfusion of fresh blood

The author studied 73 patients aged 16 79 to whom 84 treatments were given maximal duration of a treat ment was 62 consecutive days He treated 52 thromboses of the lower and 1 of the upper extremities Good im mediate results were obtained in about 80 per cent and the most noticeable improvements occurred in early treatment as in postoperative thrombosing venous com plications The 20 per cent who did not respond to treat ment or responded poorly and late included patients who had not taken the treatment regularly whose pro thrombin rate never fell below 50 per cent who had not received prolonged treatment or had associated lesions hard to influence by this treatment (old irreversible anatomic lesions of veins) Between the second and third days of successful treatment the patients called the phy sician s attention to the fact that the leg was thinner cramps had decreased in intensity and the painful radia tions along the veins had disappeared Seven patients

trolled the individual patient's prothrombin time was usually not far below his bleeding threshold In two cases vitamin K was given to raise prothrombin level and in both response was prompt bleeding being controlled in less than 24 hours There were no cases of fatal hemorrhage

Thromboembolism occurred during therapy in three patients In one it occurred while the patient's prothrombin time was within what is considered the therapeutic range whereas in the other patients it was above normal

It is concluded that dicumarol® is of value in prophylactic and active treatment of thromboembolic conditions and that results are best if prothrombin level is kept in a range of 10 30 per cent as estimated by the two stage test

Aside from bleeding no toxic effects from dicumarol® occurred and prothrombin levels promptly returned to normal when use of the drug was discontinued

New Synthetic Anticoagulant Tromexan® (G 11705) Experimental Study R Della Santa[2] (Univ of Geneva) found that the activity of this drug (ethylic ester of 4 4 dioxycumarinyl acetic acid) is evident within 3 hours after oral administration reaches its maximum in about 20 or sometimes 24 hours and stops promptly after suspension of the treatment so that physiologic prothrombinemia is usually re established in 48 hours In a subject with normal liver function prothrombin rate increases about 40 per cent in the 24 hours following cessation of medication thus guarding the patient against hemorrhagic complications However individual sensitivity to the drug varies and reversibility of the induced hypoprothrombinemia is delayed when function of hepatic cells is damaged

Tromexan® comes in 300 mg tablets divisible into halves It causes no digestive disturbances and is rapidly absorbed in the duodenum The radical treatment consists of daily administration of 1 200 mg for two to

(2) Schw iz med. Wchnschr 9 195 06 Mar 5

to establish the diagnosis of a cerebrovascular accident

Change of character particularly after a dizzy spell should make the physician highly suspicious that a small stroke has occurred After a short fainting attack or a spell of dizziness or distress in thorax and abdomen the patient s family notices a change in temperament memory or ability The patient may have lost his drive or judgment and ability to get things done In Alvarez s gastroenterologic practice patients are frequently referred because little strokes have been accompanied by some sort of storm down the vagus nerve or by distress or pain referred to the abdomen

When such small thromboses occur during the night when blood pressure is low the patient may waken with a head on him or much of his memory gone It is rare that such strokes produce muscle weakness or anesthesia because there are so many places in the brain in which a good sized area of destruction can occur without affecting motor function or sensation

Often the patient says that he fell or slipped or stumbled or miscalculated *the height of a step* but the fact that for weeks or months afterward he was confused or dizzy or unable to work makes it seem more probable that his fall was due to a slight stroke Many attacks of so called acute indigestion are really small strokes With many a small stroke blood pressure suddenly falls to normal Sometimes pressure goes back up but sometimes it does *not Sudden unexplained weight loss may be the* result of a small stroke If the bulb is affected there may be interference with swallowing ropy saliva or thickness of speech Many patients say they feel top heavy uncertain or giddy They feel that if they were to turn a corner quickly while looking up they might fall But most convincing is the sudden change in personality If there has been insanity in the family a small stroke may be followed by psychopathic changes in which the patient becomes suspicious penurious immoral or depressed Occasionally a small stroke suddenly initiates insomnia A bad taste in the mouth without any local

had had one or several pulmonary embolisms before treatment but had no recurrence during treatment An interesting fact is that early mobilization was begun in 36 patients All those who responded to treatment could be regarded cured in 17 days at the latest There were four recurrences due to insufficient treatment Suspension of treatment must be gradual to avoid possibility of a hyperprothrombinemic reaction

Della Santa treated four patients with myocardial infarct (three with acute infarction) and feels encouraged to continue use of tromexan®

Only one of six patients with degenerative arterial disorders of the lower extremities improved

Four patients with hemiplegia (three with cerebral thromboses and one with embolism of cardiac origin associated with mitral narrowing) were treated satisfactory remission of the symptoms was obtained in one with thrombosis and one with embolism but with the usual delays

Fresh acute tuberculous meningitis deserves trial treatment with tromexan® in addition to streptomycin

Contraindications are cachexia severe toxic infectious states hepatocellular lesions and hemorrhagic diathesis Except for acute nephropathies renal lesions in general do not justify abstention from tromexan® therapy

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CEREBRAL VASCULAR DISEASE

The differential diagnosis between the various types of cerebral vascular accidents can usually be made correctly and is of practical importance because the proper treatment varies with the type —Ed

Small, Commonly Unrecognized Strokes are described by Walter C Alvarez[3] (Mayo Clinic) This common disease of slow dying is almost unknown today Search of books journals and encyclopedias of medicine reveal scant mention of the syndrome and it is frequently overlooked by physicians who insist on neurologic signs

(3) Postgrad Med 4 96 103 Aug 1948

subarachnoid space but is rarely present in patients with cerebral thrombosis or embolus

Transient hyperglycemia is common A leukocyte count of over 12 000 occurs in more than half the patients with cerebral or subarachnoid hemorrhage and a count of over 20 000 is diagnostic of hemorrhage unless there is concomitant infection Spinal fluid pressure is usually normal in patients with cerebral embolus or thrombosis but is usually over 200 mm in patients with intracerebral or subarachnoid hemorrhage Spinal fluid is bloody in all patients with subarachnoid hemorrhage in 75 per cent of patients with cerebral hemorrhage and in 15 per cent of patients with cerebral embolism In cerebral thrombosis spinal fluid is clear or slightly xanthochromic Improvement may be complete within a few hours or days but usually it takes several months The extent of possible improvement should not be judged until at least six months has elapsed

In differentiation of cerebral vascular accidents from other causes of coma urinalysis blood nonprotein nitrogen determinations and sugar and spinal fluid study are of great help The head should be examined carefully for evidences of external injury Pupils and optic disks should be examined Odor of breath respiratory rate temperature pulse and blood pressure should be noted

Hemiplegia may be detected by noticing that one cheek puffs out during expiration one arm drops heavily and the paralyzed leg is not withdrawn from vigorous stimulation of the soles In absence of hemiplegia or hypertension coma due to diabetes alcoholism extra or subdural hemorrhage or drug poisoning must be considered In about half the patients with extradural hemorrhage a lucid period intervenes between two episodes of coma A skull fracture through the middle meningeal artery establishes diagnosis of extradural hemorrhage Fluctuations of consciousness skull fracture or displacement of the pineal body suggest subdural hematoma When this diagnosis cannot be excluded trephine openings should be made in both temporal regions

lesion often results from a small stroke Atypical facial pains in older arteriosclerotics sudden blindness of one eye arthritis with trophic changes in one extremity or sudden onset of fear of being left alone may all suggest the possibility that a small stroke has occurred

It is common to attribute such symptoms to spasm of blood vessels but Alvarez believes that most of them result from thrombosis Though little can be done by way of treatment it is important that the patient not be deprived of all the pleasures of living such as eating smoking walking etc No effort should be made to reduce blood pressure because reduction of blood pressure reduces blood supply to the brain If the patient is intelligent it is usually best to talk the diagnosis over with him frankly Often patients themselves know what happened to them and feel better if the physician talks honestly about the diagnosis and chances of recovery or continued living

Practical Aspects of Cerebral Vascular Accidents are discussed by H Houston Merritt[4] (New York City) A recent autopsy study indicates that cerebral hemorrhage constitutes 50 per cent cerebral thrombosis 43 per cent and cerebral embolism and subarachnoid hemorrhage small percentages of all cerebral vascular lesions Cerebral thrombosis was diagnosed more often and cerebral hemorrhage less often clinically than at autopsy

Premonitory symptoms of impending cerebral vascular accidents are infrequent Coma convulsions vomiting and headache all occur in each of the four types of cerebral vascular accidents and are therefore of little differential diagnostic value Failure of vasomotor and heat regulating centers occurs in any type of fatal cerebral vascular accident Blood pressure is usually elevated in each of the types except cerebral embolus The pupil is usually larger on the side of the lesion and there is often conjugate deviation of eyes and possibly of the head to the side of the lesion Stiff neck is almost always present in patients with hemorrhage into the brain or

(4) N w York Stat J M d 48 371 378 N v 48

dominant spinal tap is done and spinal pressure measured Marked hypertension with signs of increased venous pressure in the neck requires venesection which is done slowly not over 300 cc blood being removed at one time Unless coma is deepening and a terminal condition is obvious and if massive hemorrhage can reasonably be excluded sympathetic block is performed with the patient in reclining or semisitting position in bed

TECHNIC—The patient's neck is slightly extended by placing a small pillow under the shoulder blade of the same side head is turned away from the side of injection When an applicator dipped in iodine is drawn from the mastoid process through the tips of the palpable transverse processes to the clavicle the tip of the seventh transverse process is easily located A dermal wheal of 1 per cent procaine is made in this area and a 4 in 22 gauge needle is inserted through the wheal until it contacts the tip of the transverse process Then the needle is moved along the superior border of the transverse process until it contacts the body of the sixth cervical vertebra If no air or blood can be aspirated 10 cc of 1 per cent procaine is injected Successful block is followed within 10 15 minutes by Horner's syndrome and clinical improvement should be noted at this time These injection are repeated daily until no further improvement is noted

Of 50 patients on whom de Takats performed cervical sympathetic block 41 had a good response Improvement is attributed to relief of stasis vasoparalysis and exudation of plasma which occur in all cerebrovascular accidents in the area surrounding the ischemic or hemorrhagic infarct

Additional treatment of patients with emboli includes medication for slowing of rapid fibrillation and anticoagulants In all three varieties of apoplexy hypertonic sucrose or concentrated albumin with 0 24 0 5 Gm aminophylline given intravenously should reduce cerebral edema Respiratory tract is aspirated if mucus and bronchial secretions collect and postural drainage is instituted If after 24 hours the patient is still unconscious parenterally administered fluids are substituted by hourly feeding through a Levin tube Bladder distention is prevented by catheterization and sedation is used if the patient is hyperactive

Sudden onset of neurologic symptoms in patients with endocarditis auricular fibrillation coronary thrombosis or infection suggests cerebral embolism Primary subarachnoid hemorrhage is suggested by headache and meningeal irritation Paralysis of cranial nerves also suggests the diagnosis though focal neurologic signs occur in less than 20 per cent of cases

Treatment includes maintenance of nutrition emptying of bowel and bladder and frequent change of position Procaine injection of the cervical sympathetic trunk has been suggested Increased intracranial pressure from cerebral hemorrhage may be relieved by repeated lumbar punctures If bleeding from an aneurysm within the skull has occurred the aneurysm may be ligated proximally or on both sides of the sac Physical therapy is important after the patient has recovered from the first onslaught

Emergency Treatment of Apoplexy Geza de Takats[5] (Univ of Illinois) stresses the importance of differentiating between cerebral embolism thrombosis and hemorrhage Of 121 patients with apoplexy studied cerebral emboli was diagnosed in 15 cerebral thromboses in 53 and cerebral hemorrhage in 53 Cerebral embolus was diagnosed in the presence of a sudden cerebrovascular insult in patients with obvious cardiac source of the embolus or previous embolic episodes and clear spinal fluid under normal pressure Cerebral hemorrhage usually occurred suddenly in patients with high blood pressure and was generally accompanied by increased cerebrospinal fluid pressure and blood in spinal fluid Cerebral thrombosis was diagnosed by exclusion of embolism and hemorrhage as the cause of stroke It was usually of gradual onset in patients with cardiovascular renal disease and moderate hypertension

The earlier treatment is begun in patients with apoplexy the better are the chances for hastening restitution The patient is immediately placed in an oxygen tent If signs of increased cerebrospinal pressure are

(5) P tg d Med 5 184 190 M h 1949

and prevention of pregnancy in these patients Auricular fibrillation from rheumatic heart disease occurred in only one patient

No patient had cardiac failure during pregnancy who had not had cardiac symptoms before pregnancy 16 per cent of those with symptoms up to 10 years previously had heart failure during pregnancy and 27 per cent of those with symptoms more than 10 years decompensated during pregnancy Ten per cent of patients under 25 were in class 3 (New York Heart Association) during pregnancy among patients 25 34 19 per cent were in class 3 during pregnancy and among patients over 34 25 per cent Evans concludes that duration of cardiac symptoms exercise tolerance before pregnancy and patient s age all have a bearing on cardiac prognosis during pregnancy and that the most valuable of these is exercise tolerance before pregnancy Other useful data on such patients are heart size before and during pregnancy and cardiac history in previous pregnancies

Myocarditis Associated with Acute and Subacute Glomerulonephritis Ira Gore and Otto Saphir[7] (Washington D C) reviewed records of 160 patients with anatomically proved acute and subacute glomerulonephritis not associated with scarlet fever typhus fever or prolonged septicemia to ascertain the presence and character of any concomitant myocarditis Myocarditis was found in 16 patients Twelve had clearcut clinical manifestations of myocardial failure and two more a suggestion of clinical manifestations of heart failure

Most deaths from glomerulonephritis were attributable to heart failure The condition was recognized clinically in six patients but not in six others although records included similar clinical observations In two additional patients the recorded evidence of myocardial failure was limited to rapid development of pulmonary edema in one and striking disproportion of pul e rate and temperature in the other There were four unexplained deaths but these patients had had various mani

(7) Am H t J 36 390 40 S pt mbe 1948

Heart Disease and Pregnancy Study of 100 Pregnancies P R C Evans[6] (London) reviewed case records of all pregnant women with heart disease excluding those with hypertension in the obstetric unit of Guy s Hospital during a recent 7½ year period Among 90 whose records were investigated 40 returned for examination and 15 answered questionnaires Re examination included determination of the point of maximal impulse by physical examination and determination of cardiac symptoms Chest x rays and electrocardiograms were not made and fluoroscopy was performed only on patients with equivocal physical findings

Of 100 pregnancies studied 92 were allowed to proceed beyond the sixteenth week Types of heart disease included were 85 rheumatic 4 congenital 2 thyrotoxic and 1 questionably syphilitic Among patients with rheumatic heart disease 72 had pure mitral disease 10 had mitral disease and aortic regurgitation 2 had mitral disease aortic regurgitation and aortic stenosis and 1 had a pure aortic valvular lesion

Four of eight ascertained deaths occurred in patients with pure mitral lesions and four in patients with mitral and aortic lesions Congestive heart failure caused death in six and subacute bacterial endocarditis was responsible for one One patient died during pregnancy and two died within six months after delivery Mortality rate for patients dying within 14 months after first pregnancy was 15 per cent among multiparas it was 2 per cent

It is inferred from these statistics that when a patient survives one or more pregnancies prognosis for further pregnancies is relatively good Low mortality in this group when contrasted with previous studies is attributed to closer antepartum supervision and to recognition of high mortality in patients with auricular fibrillation

(6) G y s H sp R p 96 194 207 1947

per cent and carbon dioxide combining power 27 volumes per cent

The second hospital day transient auricular fibrillation was noted and temperature rose to 101 5 F Despite administration of sulfonamides and diuretics the symptoms became worse disorientation and incontinence gradually developed and death occurred on the eighth hospital day

The heart weighed 600 Gm and was greatly deformed by large confluent masses which almost entirely replaced both atrial walls The ventricles were not enlarged but beneath the aortic arch and partially surrounding it was a large mass of lymph node with the gross appearance of the neoplasm found in the heart The neoplasm was composed of closely packed large round cells of fairly uniform size characteristic of reticulum cell sarcoma

Review of reported cases of malignant tumors of the heart reveals no clearcut clinical entity because of the wide variation of types of tumor represented Some of the common clinical manifestations were intractable cardiac failure without obvious cause hemopericardium obstruction of the superior vena cava intermittent mitral stenosis cardiac arrhythmias and x ray evidence of cardiac deformity or a mediastinal mass Some or all of these manifestations of cardiac cancers are shared by benign tumors of the heart benign and malignant tumors of the pericardium and metastatic tumors of heart and pericardium

Anatomically the tumors are more commonly located at the base of the heart and on the right side Metastases are often found in the lungs A wide variety of histologic types have been reported the two most common being spindle cell and round cell sarcomas

Penicillin and Caronamide in Resistant Subacute Bacterial Endocarditis is described by C H Stuart Harris J Colquhoun and J W Brown[9] (Sheffield England)

Case 1—Man 28 was hospitalized with obvious subacute bacterial endocarditis superimposed on rheumatic heart disease Within 15 months he was given three courses of penicillin lasting 28 days 43 days and 3 months Total of 210 000 000 units of penicillin was given in addition 72 5 Gm streptomycin was given during a 23 day period Streptococcus viridans isolated from blood was sensitive to between 0 03 and 0 015 units

(9) La t 1 99 101 J 15 1949

festations of heart failure Evidence suggesting heart failure included cyanosis and dyspnea in 11 patients arrhythmia in 14 bradycardia in 5 hypotension in 3 weak thready pulse in 2 and ankle edema without facial edema in 2 Electrocardiographic tracings available for four patients were abnormal for three Cheyne-Stokes respiration occurred once

The increased heart weights which were observed frequently could be correlated better with the presence of myocarditis than with arterial hypertension which had been noted in only four patients The myocarditis found had a distinctive character which differentiated it easily from that occurring as a result of sulfonamide hypersensitivity or after acute nasopharyngeal and tonsillar infections Characteristically there was widespread serous effusion into interstitial tissues increasing the space between muscle fibers Cellular elements were relatively sparse and consisted of lymphocytes endothelial leukocytes and Aschoff cells The suggestion that myocardial damage is related to increased capillary permeability appears to the authors to be supported by the pathologic evidence.

It is recommended that patients with myocarditis associated with glomerulonephritis be given fluids intravenously only with great caution

Primary Malignant Tumors of Heart Report of Case More than 300 primary cardiac tumors have been reported about 100 of which were malignant Sixteen of these tumors were reticulum cell sarcomas C Merrill Whorton[8] (Boston City Hosp) reports an additional case of reticulum cell sarcoma of the heart

Woman 79 was hospitalized because of dyspnea and edema of the ankles of two weeks duration which responded poorly to digitalis Examination revealed pronounced respiratory distress cyanosis and enlargement of the heart 2 cm beyond the midclavicular line Cardiac sounds were faint but rhythm was regular There was evidence of fluid in the lungs the liver was enlarged and the lower extremities were moderately edematous Nonprotein nitrogen content of the blood was 126 mg

(8) Cancer 2:4 260 March 1949

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penicillin/ml when patient was first seen but later became so resistant that it was inhibited only by 0 125 units/ml

Because of repeated relapses during which blood cultures were positive it was decided to administer caronamide and penicillin simultaneously Penicillin was given intramuscularly in 300 000 unit doses every three hours for 39 days On the ninth day of therapy caronamide was started orally in 4 Gm doses every four hours and continued 30 days Blood penicillin levels were much higher after administration of caronamide Fever was controlled before caronamide was started but occasional emboli occurred during the first three weeks of combined therapy Nausea was alleviated by phenobarbital Edema of the lumbar region occurred after 26 days of combined therapy and persisted 10 days Six daily blood cultures at end of therapy were sterile

CASE 2—Woman 34 without previous history of heart disease was hospitalized with obvious subacute bacterial endocarditis Within 15 months three courses of penicillin totaling more than 168 000 000 units were given Despite all this treatment blood culture became positive again Isolated Str viridans had been sensitive to 4 units penicillin/ml at onset of treatment and after this period was still sensitive to 8 units/ml

A fourth course of penicillin was instituted with 1 000 000 units given every six hours After nine days caronamide was started orally 4 Gm every four hours Nausea was not troublesome After nine days of combined therapy fever pains and malaise began On the twenty first day fever persisted leukocyte count had fallen to 3 000 and caronamide therapy was suspended penicillin was continued another six days Slight edema of the back was noted During the next few days improvement occurred and temperature became normal Three successive daily blood cultures were sterile one week later and the patient remained well for five months

CASE 3—Girl 18 was hospitalized because she was thought to have recurrent acute rheumatic fever After four weeks subacute bacterial endocarditis became apparent Streptococcus viridans was found in blood culture Penicillin 1 000 000 units every three hours was given for almost three weeks and sulfadiazine was also given Because no improvement occurred caronamide was administered in 4 Gm doses every four hours for three days Temperature became normal Caronamide was stopped because of nausea and lumbar discomfort but penicillin was continued another two weeks Patient remained well and was at work six months later

Although caronamide is not thought to be toxic to normal kidneys edema occurring in th

gests that it might impair function of kidneys already damaged by subacute bacterial endocarditis

Streptomycin in Acute Tuberculous Pericarditis Case Report is presented by H Clarkson Meredith Jr [1] (Univ of Virginia)

Negro boy 17 was hospitalized because of fever dyspnea and a fluctuant mass 4 cm in diameter which had been present in the neck for five months It had been incised by his physician and a draining sinus resulted Temperature was 103 2 F pulse rate 100 and blood pressure 106/70 Both axillae contained nodes 2 cm in diameter There were dulness and diminution of breath sound in the left chest below the second rib anteriorly and somewhat lower posteriorly Left border of the heart was in the left anterior axillary line and right border of the heart extended 2 cm to right of the sternum X rays revealed tremendous enlargement of the heart and fluoroscopy howed no pulsations There was no evidence of pulmonary tuberculosis in the chest at this time An electrocardiogram showed slurred QRS complexes and low or inverted T waves

Cardiac tamponade became apparent on the third day and 500 cc of port wine colored fluid was removed by pericardial paracentesis Relief of dy pnea substernal pressure anxiety and tachycardia was dramatic

Tubercle bacilli could not be found in sputum gastric washings or pericardial fluid but caseous tuberculosis was found in biopsy of an axillary node Fever and tachycardia continued On the twentieth day streptomycin 200 mg every three hours was started and continued for 33 days the patient was observed for 10 days after drug was stopped Temperature began to decline two days after tart of treatment reached normal in four or five days and remained there until the patient s discharge to a tuberculosis sanatorium after 62 days of ho pitalization At time of discharge he felt well was eating well had gained 17½ lb and wanted to return to work A chest x ray made at the sanatorium showed exudative tuberculosis in the left lower lobe previously obscured by pericardial effusion

Histories of two other patients with tuberculous pericarditis treated successfully with streptomycin have recently been reported

Cellophane Treatment of Syphilitic Aneurysms with Report of Results in Six Cases is described by J K Poppe (Portland Ore) The intense foreign body reac

(1) Am H t J 37 1 9 133 J y 1949
(2) Ibid 36 252 256 A g t 1948

tion produced by Cellophane with its constricting fibrosis has been used for almost 10 years for gradual obliteration of the lumen of large blood vessels Disagreement arose because of reports that Cellophane produces no foreign body reaction This question has been settled by finding that some Cellophane products produce foreign body reaction whereas others do not Poppe chose impure Polythene Cellophane because of its ability to produce fibrosis

Aneurysms of the thoracic aorta were treated by operating through a paravertebral incision extending around the angle of the scapula The entire length of the fifth or sixth rib was resected and the aorta freed Often it was impossible to free the entire circumference of the descending aorta because of erosion of vertebra and ribs A sheet of Polythene Cellophane was then cut to fit the dilated portion of the aorta The Cellophane was sutured loosely to any suitable mediastinal tissue with fine silk sutures care being taken not to pass any sutures directly into the aneurysm wall

Six patients all with syphilitic aneurysms of the thoracic aorta were so treated Two were operated on so recently that it was impossible to evaluate results but in the other four results were good All four patients were relieved of chest pain during follow up ranging from a few months to two years

The chief purpose of Cellophane wrapping of aneurysms was to prevent further expansion and eventual rupture or erosion into adjacent vital structures It was not anticipated that pain would be relieved No autopsy material is available to determine whether or not the lumen shrank No shrinking was detected on x ray possibly because the x ray shadow of the aorta increased in size because of the fibrosis Results were best in fusiform aneurysms of the descending thoracic aorta where it was possible to encircle the aneurysm completely without encountering other vital structures

Contraindications to the operation appear to consist of bronchial obstruction or erosion fro ressure se

vere heart disease with aortic insufficiency and decompensation or erosion of the anterior chest wall Arteriosclerotic aneurysms are less suitable than syphilitic aneurysms for surgery because of the generalized distribution of arteriosclerosis and the advanced age of patients with this condition

Mechanism of Arterial Hypotension during Anaphylactic and Histamine Shock in Rabbit According to Pasteur Vallery Radot B N Halpern and G Mauric[3] (Univ of Paris) the most specific and constant sign of anaphylactic shock in the rabbit is arterial hypotension accompanied by splanchnic and peripheral vasoconstriction The hypotension could be explained by diminished blood return to the heart from pulmonary and portal systems To study pulmonary circulation rabbits were anesthetized with urethane and the great vessels exposed through a unilateral thoracic opening (and unilateral pneumothorax) It was possible to maintain adequate respiratory exchange with the uninjured hemithorax Water manometers were connected by way of heparinized Ringer s solution to glass cannulas inserted into carotid and pulmonary arteries and pulmonary veins Pressure change was measured after injection of horse serum to which the rabbits had been made sensitive several weeks before after histamine and after preliminary injection of antihistaminic drugs

Injection of serum into sensitized rabbits caused an immediate significant rise in pulmonary artery pressure due to pulmonary vasoconstriction This appeared to be independent of the degree of arterial hypotension measured in the carotid artery Pressure in the pulmonary vein dropped Histamine even in small doses caused considerable elevation in pulmonary arterial pressure and a similar fall in pressure in the pulmonary vein These hemodynamic alterations caused no regular effect on carotid pressure *Histamine effect on pulmonary artery pressure* is not due to cardiac effect since it is also found in perfused lungs Antihistaminic compounds (antergan ® neo

antergan® and N dimethylamine 2 propyl 1 thiodiphenyl amine) totally suppress histamine effect on pulmonary circulation although drop in carotid pressure still follows histamine

It is impossible in view of these experiments to attribute systemic hypotension following anaphylactic or histamine shock to pulmonary hypertension

Worker with Cardiac Disease in Industry Harold H Steinberg[4] (Chicago) points out that physicians should attempt to keep persons handicapped by cardiac disease employable and self sufficient Often the physician in industry is guided principally by his desire to protect the employer from employing persons prone to disability from illness or accident But approached intelligently industry is usually willing to assume its role in rehabilitating disabled persons During World War II it was found that many persons previously disabled by heart disease were employable and productive

To the layman and often to the physician heart disease connotes invalidism If this situation is to be corrected several problems must be considered Persons with heart disease must be placed in suitable jobs and given medical supervision while at work Heart disease should be recognized early in previously healthy workers so that treatment can be instituted Acute cardiac emergencies such as coronary occlusion acute heart failure and dissecting aneurysms must be diagnosed accurately and after adequate convalescence patients should be returned to jobs consistent with their abilities To accomplish these aims there must be co operation between the physician in industry the patient s own physician the specialist in internal medicine or cardiology management labor and the patient himself

The physician must not only appraise the patient s physical status but must understand the demands of the specific job These demands may be physical emotional or environmental One simple method of evaluating a job includes provision by the employment department

(4) Occup M d 5 186 193

of a simple job description for the physician This can easily be attached to the physical examination form The industrial physician should periodically go into the plant to appraise specific jobs

The physician s opinion should be determined from what the heart can do rather than by the nature or character of heart murmurs Previous bouts of decompensation or disability from cardiac dysfunction enlargement or gross failure are significant evidence of disability Exercise tests seem of little value

In one plant employing 6 500 7 000 persons significant hypertension was found in 74 These persons continued to work in all types of jobs except those involving operation of moving machinery and work above ground level Of the 74 persons 45 have been observed 10 years for hypertension and of these over half have not lost a day because of hypertension

Certain jobs such as that of foreman or work in foundry hammer shop and forge may predispose to elevation of blood pressure because of job responsibility tension or noise

There appears to be little correlation between occupation and incidence of coronary occlusion and return to work after coronary occlusion has not been found to increase significantly the occurrence of further episodes In the industry described 15 employees were working after episodes of coronary occlusion and 7 were working with aortic aneurysm In addition many workers had angina pectoris All these persons were examined yearly but job transfer was rarely recommended because maintenance of earning power and pride in one s own trade were recognized as important factors in maintaining adequate cardiac function

The Digestive System

GEORGE B EUSTERMAN M.D

PART V

THE DIGESTIVE SYSTEM

ESOPHAGUS STOMACH AND DUODENUM

The literature of the past year pertaining to this department, as heretofore has been voluminous so that the selection of representative articles of current interest as well as noteworthy contributions of original nature has not made my task difficult. I have included more editorial comments than usual in compliance with a recent request from some quarters which I hope will meet with the approval of our readers —Ed

Benign Stricture of Esophagus Special Reference to Esophagitis Hiatus Hernia Esophageal Ulcer and Duodenal Ulcer Edward B Benedict and Richard H Sweet[1] (Massachusetts Gen l Hosp) report on 60 cases all based on esophagitis Esophagitis appeared alone in 18 cases with hiatus hernia in 34 with duodenal ulcer in 20 with esophageal ulcer in 16 and with the last three conditions concomitantly in 6 Regurgitation of acid gastric secretions probably played an important role

The outstanding symptom of benign esophageal stricture is dysphagia of varying degree Regurgitation hematemesis heartburn anorexia and inability to belch may be noted Diagnosis is based on history x ray examination and esophagoscopy Differentiation from carcinoma is most important For this purpose esophagoscopy and biopsy are essential In doubtful cases in which biopsy is negative the procedure should be repeated until a satisfactory specimen is obtained from deep within the lumen of the stricture

Bouginage combined with dietary treatment gave satisfactory results in two thirds of 43 cases Bouginage should be carried out at the time of the first esophagoscopy and every time esophagoscopy is repeated for ad

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[1] [illegible]enterology 11 (184 8 [illegible]vember 1948

ditional biopsy material If dysphagia continues the patient is asked to swallow a thread which is used as a guide to further bouginage A bland diet of liquid and strained food as tolerated is important Frequent feedings are indicated Antacids may be useful Alcohol and tobacco are interdicted

Failure of bouginage is the indication for surgery It is better for the elderly patient who is a poor surgical risk to eat strained foods than to undergo major surgery Recurring attacks of dysphagia with pain and hemorrhage from an esophageal ulcer uncontrolled by diet and bouginage are good indications for surgery in a good risk patient The danger of malignancy as an indication for surgery has been overemphasized since a good esophagoscopist can rule out malignancy by biopsy For most patients resection is the operation of choice since plastic repair is difficult because of the inflammatory nature of the disease and length of the stricture Of the patients treated surgically 3 had excellent results with a plastic procedure 12 were completely relieved of symptoms by resection 1 patient died after resection and in 1 a stricture developed after resection

Gastric Resection for Esophagitis and Stricture of Acid Peptic Origin Owen H Wangensteen and N Logan Leven (Univ of Minnesota) present experiences with six patients who had esophagitis or esophageal stricture or both and in whom gastric resection relieved esophageal obstruction Four patients had esophagitis three of whom had duodenal ulcer and severe concomitant complications Another had a congenitally short esophagus with stricture and had had gastric hemorrhage The remaining patient had had trouble in swallowing since childhood the difficulty became progressive eventually necessitating frequent dilatation In four of the other patients esophageal dilatation was carried out frequently

Ulcer is observed most frequently in the duodenum probably because it is the sole exit through which gastric

( ) S g Gynec & Obst 88 560 570 M y

juice escapes from the stomach Regurgitation of acid digestive juice into the lower part of the esophagus is not uncommon as manifested by the frequency of eructation or substernal burning sensation If all gastric juice left the stomach via the esophagus esophagitis would probably be the most frequent clinical type of ulcer Hiatus hernia not only is frequently associated with gastric ulcer but may be a forerunner of esophageal ulcer Since esophagitis may be the only manifestation of ulcer every patient with this condition should be questioned about periodic sensation of burning in the esophagus acid eructations and tasting of food long after its ingestion substernal pain difficulty in swallowing and pain on swallowing If at x ray examination great care is taken to note any abnormal behavior of the lower part of the esophagus such as spasm persistent narrowing or halting of the forward progress of the barium column into the stomach esophagitis will be recognized more frequently

Effective gastric resection is suitable for relief of esophageal obstruction arising as a manifestation of ulcer disease because it reduces acidity and digestive capacity of juice secreted by the residual gastric pouch and quickens gastric emptying time After operation digestive juices lose their capacity to irritate the esophagus and the need for continual esophageal dilatation disappears after normal diameter is re established

[This is an original and valuable contribution Fortunately such complication in the large majority of ulcer bearing patients especially in its more severe form is unusual in my experience In future cases if circumstances would permit a study of the nocturnal gastric secretions from the standpoint of volume concentration and amount of hydrochloric acid would be of interest Extensive gastric resection would seem to be too heroic treatment in the absence of a refractory or complicated gastroduodenal ulcer —Ed]

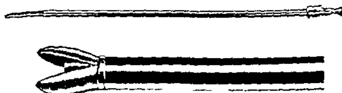
Construction and Use of Safe Diagnostic Optical Esophagoscope The instrument developed by Rudolph Schindler[3] (College of Med Evangelists) consists of an outer tube with obturator (Fig 97) an inner tube with two spreading shells at its tip (Fig 98) and an optical

[3] Gastroenterology 1 355 367 March 1949

tube which may be exchanged for a biopsy forceps

The outer tube is 10 mm in diameter and 46 cm long The diameter permits use of the instrument in children It reduces discomfort to a minimum and increases safety to a maximum The obturator is a 6 cm rubber finger attached to a metal rod which fits tightly into the tube and projects from it a few millimeters thus avoiding free edges

The inner tube fits tightly into the outer tube and has two movable shells which can be spread to a diameter of 15 mm (Fig 98) by action of a wheel at the oral end



Fg 97 (t p) —O t r t b w th obt at r
Fg 98 (b tt m) —T p f ne t be w th shells open T p of opt al t be v ble
(Court y f S h ndle R Gast o nt ology 12 355 367 Mar h 1949)

After removal of the obturator the inner tube is intro duced into the outer tube a maneuver facilitated by a cutout of the upper end of the outer tube

The optical tube usually introduced with the inner tube consists of an optical system light carrier and two air channels The optical system is an objective without prism plus an erector system and eyepiece The light carrier consists of a long metal tube with a small elec tric lamp which may be connected by a detachable cable to any simple electric battery The air channels are sim ple hollow tubes attached at the sides of the light carrier and are connected with an attachment for an air balloon or suction apparatus

The biopsy forceps consists of an optical tube joined solidly to a light carrier and to the outer of two cun

bearing jaws of cutting forceps The inner jaw is attached to a tube which slides up on the optical tube when the instrument handle is closed The biopsy forceps lies loosely within the inner tube It can be advanced about 2 cm into the lumen of the esophagus through the opened hells Taking of biopsies is not difficult

The only new instructions in connection with use of this instrument concern positioning of the patient For diagnostic esophagoscopy left lateral position with freely movable head in combination with reverse Trendelenberg position is recommended Whether this position will be useful in therapeutic esophagoscopy is not known

Burning Sensation of Tongue (Glossodynia) Analysis of Cases Not Due to Vitamin B Deficiency Samuel Waldman and Louis Pelner[4] (Brooklyn) report seven cases of burning of the tongue and dryness of the mouth due to thickening of saliva In some saliva was so tenacious that it appeared as thin strings stretching from soft palate to tongue Smoking was considered a contributory factor in several cases Because parasympathetic stimulation facilitates salivary secretion it was decided to administer 7 5 mg prostigmin[*] bromide three times daily after meals A copious thin salivary secretion resulted and burning and dryness diminished or disappeared A large fluid intake was prescribed and if smoking was thought to be a factor it was interdicted

In making a diagnosis one must consider niacin and riboflavin deficiencies pernicious anemia Plummer Vinson syndrome irritation from food drink or smoking and electrogalvanic currents produced in saliva by dissimilar metallic dentures in some instances burning may be only a symptom of thrombosis of a small intracranial vessel It may be associated with the menopause or psychoneurosi

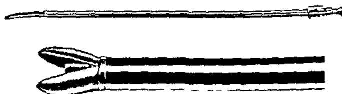
Heartburn Clinical Study Henry J Tumen and Edwin M Cohn[5] (Philadelphia) studied 120 consecutive office patients referred for a variety of gastrointestinal

t oe te logy 10 965 969 J 1948
M A. 139 292 298 J 29 1949

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F g 97 (t p) —O te t b w th bt at
F g 98 (b tt) —T p of n er t be w th shell open T p f optic l t be bl
(C te y f Sch dl r R G t oent logy 12 355 367 M r h 1949)

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tonus of the lower part of the esophagus Questioning of the 74 patients without heartburn revealed that only 9 were in the habit of eating fast gulping food and washing it down with large quantities of water On the other hand many patients with heartburn have bad eating habits Heartburn in eight patients was possibly a psychosomatic manifestation and an expression of tension and emotional disturbance Only one patient without heartburn had a personality pattern similar to that observed in this group

In treatment of heartburn it is important to outline a general program which will remove the cause if any can be found and allay the irritability of the esophagus and stomach as well as help the patient understand the nature of his problem Drugs were of little use and were used infrequently Belladonna and antacids were given in selected instances Aside from the dietary regulations necessary for treatment of ulcer if this was present diets were changed only to the extent of eliminating foods which experience had indicated would cause discomfort When necessary constipation was relieved largely by instruction in hygienic bowel habits The most significant phase of treatment was discussion with the patient regarding his problem explanation of its functional nature education in proper eating habits and when necessary adequate psychotherapy All 46 patients obtained definite relief under such a regimen although some had recurrences of heartburn with extreme nervous tension

[Investigations directed to the possible cau e and treatment of such minor di orders as heartburn and a burning sensation of the tongue or other disturbances of th s organ are commendable Such disturbances are exceedingly common and can be very troublesome and eas ly ignored in the over all consideration of the patient s various complaints Although the authors admit that additonal studies are need d to expla n the mechanism causing heartburn they are convinced that this disorder is caused n all probability by abnormal neuromuscular act v ty at or just above the cardia with alteration of esophageal tonus In a discu sion follow ing the presentation of th s paper the importance of not overlooking such organic cond t ons as hiatal hernia especially congenitally short esophagus duodenal ulcer and cholecystic disease

disturbances and found that 46 complained of heartburn In 26 it was severe enough to be considered a major symptom but in none was it the only reason for seeking medical care Heartburn was usually described as a sensation of burning or heat behind the lower part of the sternum When severe it tended to spread up along the esophagus frequently to the pharynx and even to the angles of the jaw Some patients found the sensation and location difficult to describe The most frequent time for heartburn to begin was shortly after a meal particularly a large one eaten rapidly Many patients noted no relation to food intake Associated gastrointestinal symptoms were frequent and varied but acid regurgitation belching nausea and epigastric pressure were most troublesome

Nervous tension was the outstanding immediate cause of heartburn almost 75 per cent of the patients recognized that it was worse during emotional strain Fatigue sensitivity to specific foods the acts of eating or smoking use of alcohol and constipation were implicated by some patients

About half the patients were relieved on taking sodium bicarbonate The majority had used proprietary antacids with variable success No consistent relation was noted between the relief from antacids and the amount of hydrochloric acid in the stomach The fact that 25 patients were not relieved by taking antacids suggests a lack of relation between occurrence of symptoms and amount of acid Changes in esophageal tonus which follows induced belching may explain the relief given by sodium bicarbonate

Patients with gastric or duodenal ulcer irritable colon syndrome and cholelithiasis had no significant incidence of heartburn Hiatal hernia was the only organic condition with which heartburn was associated with outstanding frequency Gastric analyses in 31 of the patients did not disclose a relation between hyperacidity and heartburn

Heartburn is probably produce

tonus of the lower part of the esophagus Questioning of the 74 patients without heartburn revealed that only 9 were in the habit of eating fast gulping food and washing it down with large quantities of water On the other hand many patients with heartburn have bad eating habits Heartburn in eight patients was possibly a psychosomatic manifestation and an expression of tension and emotional disturbance Only one patient without heartburn had a personality pattern similar to that observed in this group

In treatment of heartburn it is important to outline a general program which will remove the cause it any can be found and allay the irritability of the esophagus and stomach as well as help the patient understand the nature of his problem Drugs were of little use ind were used infrequently Belladonna and antacids were given in selected instances Aside from the dietary regulations necessary for treatment of ulcer if this was present diets were changed only to the extent of eliminating foods which experience had indicated would cause discomfort When necessary constipation was relieved largely by instruction in hygienic bowel habits The most significant phase of treatment was discussion with the patient regarding his problem explanation of its functional nature education in proper eating habits and when necessary adequate psychotherapy All 46 patients obtained definite relief under such a regimen although some had recurrences of heartburn with extreme nervous tension

[Investigations directed to the possible cause and treatment of such minor disorders as heartburn and a burning sensation of the tongue or other d sturbances of thi organ are commendable Such disturbances are exceedingly common and can be very trouble some and easily ignored in the over all consideration of the pa t ent s va ious complaints Although the authors admit that addi t onal studies are needed to explain the mechanism causing heart burn they are convinced that this disorder is caused in all proba bility by abnormal neu omuscular activity at or just above the cardia with alteration of esophageal tonus In a discussion follow ng the p esentation of this paper the importance of not over looking such organic condit ons as hiatal hernia especially con gen tally short esophagus duodenal ulcer and cholecystic disease

was emphasized by others Even in the presence of such lesions the authors felt that they are coincidental and not the cause of heartburn Physiologic research has shown that gastric hyperactivity in response to stimuli arising out of situational stress is frequently associated with heartburn to say nothing of epigastric pain which in quality time of appearance following alimentation and mode of relief closely if not absolutely approximates the ulcer pattern Conversely gastric hypoactivity of emotional origin is accompanied by a sensation of epigastric fulness and nausea —Ed]

Proof of Hormonal Mechanism for Gastric Secretion —Humoral Transmission of Distention Stimulus Proof for the existence of a hormonal mechanism for gastric

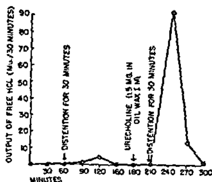


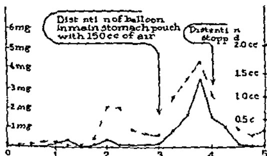
Fig 99 —R d f e pe m nt on d g with t a planted pylo pou h and f t l of man stom h h w g e tion f c d by man tom h n r sponse to d t nt n f t a pl t d po ch R spo e was sm ll befo e i jec t n f ure h l Ue h l ne alone d d n t stimulate g str c ec et n but g e tly p tent ted secr t y e pon to ubsequ nt d tent on of p lo c pouch (Courtesy f G os m n M I et al Am. J Phy ol 153 19 Apr l 1948)

secretion has until now been lacking Two kinds of stimuli acting in the stomach are effective in evoking gastric secretion namely chemical and mechanical (distention) That the chemical stimuli can be humorally transmitted has been well known but it has been thought that the distention stimuli was not humorally transmitted

M I Grossman C R Robertson and A C Ivy[6] (Univ of Illinois) performed *experiments* which indicate that distention of the pyloric portion of the stomach stimu

(6) Am J Phys 1 153 19 Ap 1 1948

lates secretion of hydrochloric acid by the fundic glands This effect still occurs when all nerve connections between the stimulated portion of the stomach and the portion responding with secretion have been interrupted This interruption can be accomplished by subcutaneous transplantation of either the part of the stomach which is to be stimulated the pyloric portion (Fig 99) or the part which responds to the stimulus the fundic portion (Fig 100) This demonstration of the humoral transmission of the distention stimulus is considered to consti



Fg 100—R c d f e pe m t d g w th tr pl t d fu d po ch a d pou h f m l f t ma h h w g a d sec t ry po e of tran p ted pou h t d t t on st m l a appl d to ma stoma h po h Lon u l d t utp t of f hyd ochl d fr m t pl nt d f d c pou h m ll g m Brok n l d c t s l me cub ent meter (Courtesy of C man M I t l Am J Physiol 153 1 9 Ap il 1948)

tute conclusive evidence for the existence of a hormone for gastric secretion

Nervous and Humoral Control of Gastric Secretion According to Georg Kahlson[7] (Univ of Lund) animal experiments indicate that on stimulation of the vagus nerves some active agent or agents is liberated from the pyloric mucosa which carried by the blood stream stimulates gastric glands to secrete acid juice Purification of pyloric mucosa extracts indicates that the active principle is a protein like water soluble substance (gastrin) isoelectrically precipitated at pH 4 5 5 Chemically

(7) B t M J 1091 1095 D 25 1948

gastrin closely resembles secretin It is effective only when injected directly into the blood stream Purified preparations of gastrin do not contain histamine in detectable amounts

When gastrin is given intravenously, secretion begins in about five minutes gradually increases for 5 10 minutes then proceeds at a more or less constant rate If injection is interrupted secretion continues for 10 15 minutes then gradually declines and reaches the basic level about 30 minutes after the end of injection Total acidity of the gastric juice secreted usually exceeds 150 m Eq L The peptic power of the juice declines to a very low level during the course of secretion indicating that gastrin specifically activates only the parietal cells Salivary pancreatic peptic or bile secretion gastric motility blood sugar and blood pressure are not influenced by intravenous injection of doses which cause copious secretion of gastric juice

In cats dogs and pigs gastrin is predominantly present in the pyloric mucosa In man it is localized in the pyloric and duodenal mucosae

The role of histamine in stimulating gastric secretion cannot be that of a hormone carried in the blood to all parts of the body It is possible that after gastrin is carried by the blood to the fundic mucosa it causes some change so that histamine is liberated in quantities sufficient to stimulate the parietal cells

From the experimental evidence Kahlson concludes that gastrin is a common factor in the nervous gastric and intestinal phases of acid gastric secretion

Physiologic Studies on Stomach of Woman with Gastric Fistula Russell J Crider and Sheppard M Walker[8] (Washington Univ) carried out studies on a woman 21 who inadvertently had swallowed lye and was treated by gastrostomy The wound subsequently became infected and broke down resulting in an opening 6 cm in diameter lateral to the left rectus muscle Gastric motility was cyclic but intervals between cycles and mag

(8) Arch Surg 57 19 and 1017 July 1948

nitude of contractions varied considerably Higher rhythmic waves of contractions advanced toward the antrum and were peristaltic while irregular contractions of lesser magnitude were of mixing type When the patient was happy and co operative the mucosa was red and the secreting stomach moderately active Decreased motility diminished secretions with lower hydrochloric acid content and blanching of the mucosa were associated with anger resentment fear and anxiety Sleep and menstruation had little effect on stomach behavior Secretion and color were unchanged by painful stimuli but motility was increased Cardiac sphincter stimulation caused a reflex of bile stained secretion retching nausea and heartburn Under sustained emotional tension male patients previously studied had shown hypersecretion and hypermotility neither of which were present in this patient under similar conditions

Solutions of either hydrolyzed protein (amigen®) or crystalline amino acids given intravenously decreased gastric motility secretion and pepsin production but solutions of dextrose or sodium chloride caused only slight decrease in acid and pepsin production

Doses of Histamine Producing Minimal and Maximal Gastric Secretory Responses in Dog and Man. In their work with dogs M E Hanson M I Grossman and A C Ivy[9] (Univ of Illinois) found that vagotomy does not alter the response to histamine since the vagotomized pouch of the entire stomach and the intact stomach show essentially the same response to this agent After vagotomy respon e to histamine in peptic ulcer patients is greatly depressed Therefore unless such patients differ from normal subjects it must be concluded that vagotomy produces different effects in man than in dogs

Histamine injected subcutaneously is not inactivated during its absorption from the subcutaneous tissues into the blood because stimulation of gastric secretion equals that produced by the same amount of histamine given intravenously The threshold dose of histamine for in

r hy 1 153 42 58 M y 1948

travenous administration in man is about one tenth that in dogs. This indicates that human beings are much more sensitive to histamine than are dogs.

The parietal cell is more sensitive to histamine than any other cell in the intact body. In some instances its sensitivity may be equaled by that of the cells of the cerebral vessels. Histamine probably causes acid secretion mainly by a direct effect on the parietal cell. Although no direct proof exists for participation of histamine in the normal mechanism of the gastric secretion either as a humoral agent or as a local chemical mediator, neither of these possibilities is disproved by the available evidence.

Life Situations, Emotions and Gastric Function. Stewart Wolf and Harold G. Wolff[1] (Cornell Univ.) observed disturbances of stomach function in response to threatening situations in four men with gastric fistulas. The disturbance patterns were characterized by hyper- or hypofunction of the stomach. The same person may display either pattern in varying circumstances. A person may respond in a characteristic way if conditioned by earlier experiences productive of that particular pattern. The response of the stomach may be great enough to modify or obliterate the effects of various foods or drugs.

Gastric hypofunction accompanying fear or dejection was associated with diminished flow of saliva and gastric juice. Disgust or guilt with feelings of rejection caused nausea, pallor, absence of contractions, diminished acid secretion and increased mucus output.

Gastric hyperactivity was associated frequently with heartburn and gnawing epigastric pain. This was usually relieved by taking food, milk or alkalis. In one patient vagotomy eliminated the gastric hyperactivity which occurred when he was angry, *hostile and frustrated*.

Hyperemia of the gastric mucosa was associated with increased acid production and increased motor activity. Mucosal pallor was accompanied by a diminution of these functions.

(1) Am. P act 3 1 14 September

The pattern of gastric hyperfunction may indicate a symbolic need for nourishment and sustenance at times of stress Cannon suggested that hypofunction without nausea is part of a biologic pattern of mobilization for action in which during an emergency the stomach and digestion can wait When associated with nausea and vomiting the pattern of gastric hypofunction may indicate a need for riddance an effort to reject noxious experiences

Changes in Gastric pH Following Administration of Fruit Juice to Patients with Gastric Ulcer were studied by John D Yeagley and David Cayer[2] (Bowman Gray School of Medicine) After administration of orange juice buffering of gastric acidity was noted in about half the patients Becau e many patients complained of discomfort after ingestion of fruit juices alone it was concluded that the buffering action was of short duration In 90 per cent of 19 patients with active peptic ulcers orange juice had a stimulating effect on gastric secretions and at the end of one hour pH values fell below fasting and after breakfast levels

Decrease in gastric acidity 30 minutes after administration of milk was noted in 94 per cent of ulcer patients At the end of one hour only 42 per cent still showed evidence of buffering The buffering action of milk was more prolonged than that of fruit juice but was still relatively short and must be maintained by frequent feedings None of the ulcer patients had any subjective discomfort after administration of milk even when the nature of the ingested substances was not made known

Because of the stimulating effect of orange juice and other fruit juices on gastric secretions it is recommended that they be given with regular meals or in combination with other foods when added to the diet of patients with peptic ulcer

Vascularization of Human Stomach Preliminary Note on Shunting Effect of Trauma By injecting radiopaque substances into vessels of cadavers stomachs and taking

(2) N th Ca l M J 9 555 561 N mb 1948

microarteriographs A F Barclay (Nuffield Inst for Med Research Oxford) and F H Bentley[3] (Univ of Durham) showed that larger arteries divide in gastric walls to form a plexus of smaller arteries in the submucous layer which extends over the whole gastric wall The anastomoses are large can be readily seen and are so profuse that injection of a single gastric or gastro epiploic artery fills the whole vascular plexus of both anterior and posterior gastric walls and also the other gastric and gastroepiploic arteries by retrograde flow

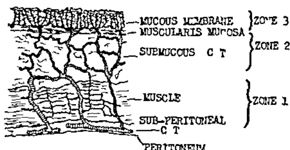


Fig 101 —D g am f om m l l m osc p c d sect on red d f m × 10 of n ject d c d tor h n wh h w g t h gh ap l a ca th bef ope t ll th zo h d bee j ct l Zo l h w m sel tom s g s bpe it l a d m scul l y r Zo 2 i l at xt a t m f mall sel subm ou ect t e In th se v sel h t pe t w t h g tl l pply the d ctly t a k i t s r t pe ph r l l t Zone 3 p t l m m mb (Cou t y of B cl y A F d B ntl y F H G t oe te log 12 177 183 F b rua y 1949)

(Fig 101) An injection mass of smaller particle size demonstrates smaller vessels arising from the main plexus and running through submucosa and muscularis mucosa toward the under aspect of the mucous membrane where they anastomose with each other to form an intricate plexus of finer vessels close to mucosa (Fig 101) From this plexus arises the rich vascular network supplying the mucosa made up of large numbers of fine arterioles which break up into capillaries that run perpendicularly through the mucosa toward the surface

When arteries of pieces of stomach removed at opera

(3) G t oent logy 1 17 183 F bru y 1949

tion were injected by the same technic it was difficult to find an area of mucosa in which the injection mass had reached the peripheral circulation This difficulty occurred in 12 specimens and suggested presence of an arteriovenous anastomosis or shunt in the submucous plexus Subsequent observations showed that veins coursing along the anterior stomach wall changed from purple blue to dusky pink during the first two to three minutes after the peritoneum was opened Percentage of oxygen saturation of blood taken as soon as possible after the peritoneum was opened and three minutes later was 74 and 91 respectively Such a rapid change in oxygenation was further evidence of direct passage of blood from the arterial to the venous side through a shunt Blocking the sympathetic outflow during operation resulted in extensive circulation through the mucosa in contrast to its absence when sympathetic pathways were intact indicatin that the arteriovenous anastomoses are under control of the autonomic nervous system

Apparently the shunt in the stomach wall is similar to that in the kidney described by Truetn and others

[In an editorial comment in the same issue of *Gastro nterology* Alvarez said that such mechanism (arterial hunt) could a ily explain the sudden formation of peptic ulcers especially of acute penetrating or perforating nature Also the shunt m ght explain those deep or perforating acute ulcers which are seen so commonly in person who die of a brain tumor or after an operation on brain or highly toxic goiter I am reminded of another mechanism apparently capable of producing such acute phenomena Cultures of virulent strain of green producing streptococcus i olated from dental granulomas in ulcer bearing patient wh n intravenously injected into dogs can give rise to acute fulminating perforating les ons —Ed]

Histologic Basis for Anacidity in Gastric Disease
Lewis W Guiss and Fred W Stewart[4] (Memorial Hosp New York City) studied the production of hydrochloric acid number of normal appearing parietal cells and degree of gastritis in 32 stomachs resected for duodenal ulcer 19 with prepyloric ulcers 20 with peptic ulcer of the body of the stomach 92 with carcinoma arising in

the pyloric gland area and 113 with carcinoma involving the fundus gland area As the intensity of chronic atrophic gastritis in the fundus increased there was proportionate decrease in number of parietal cells Production of hydrochloric acid in the stomachs of ulcer patients was proportional to the number of parietal cells present The same relation held for production of hydrochloric acid in the cancer bearing stomachs

No correlation could be obtained between location of the lesion of gastric cancer and production of free hydrochloric acid In general the gastritis in cancer of the stomach was pangastritis Therefore the degenerative changes in the fundus mucosa and the parietal cells were of the same intensity regardless of location of the cancer Also because of pangastritis little or no relation was found between size of the lesion and free hydrochloric acid except that when the lesion was large enough to destroy the major portion of the fundus mucosa anacidity naturally resulted

With peptic ulcer of the duodenum and antral area the fundus was usually devoid of chronic atrophic gastritis With peptic ulcer of the fundus gland area moderate gastric changes were found in the fundus mucosa The *figures for free hydrochloric acid closely paralleled* this incidence of gastritis with reference to location of the lesion

Figures for free hydrochloric acid obtained by gastric analysis may be considered a valuable index to the degree of degenerative gastritic change in the fundus of the stomach

Effect of Some Common Gastric Drugs on Motility of Stomach was studied by Pekka Brummer and Alfred Bundul[5] by means of x ray examinations on 137 patients The drugs included atropine sodium barbital papaverine hydrochloric acid and five antacids (sodium bicarbonate calcium carbonate magnesium carbonate magnesium oxide and ventracon[*]—a preparation containing aluminum hydroxide calcium phosphate mag

(5) A ta med Sc d na 130 559 574 1948

nesium peroxide and bolus alba) Drugs were administered orally generally in the usual therapeutic doses Control x rays were made before administration Bundul who examined the x rays made after drug administration had no knowledge of the drug used in the specific case being examined

Results indicated that atropine decreased and sodium barbital increased gastric peristalsis After a dose of 0 05 Gm papaverine no change could be observed whereas 0 1 Gm papaverine decreased peristalsis and tone of the duodenum particularly the duodenal bulb even this dose had no effect on gastric motility Hydrochloric acid had no distinct effect on gastric motility but did increase duodenal peristalsis causing in particular retroperistalsis Among the antacids sodium bicarbonate clearly increased gastric peristalsis which was also true though to a less marked degree of the other antacids used Magnesium salts in addition increased duodenal peristalsis

The authors believe that the benefit derived from the drugs studied is due to their effect on gastric and duodenal motility This opinion is supported by experiments with antacids in which it was established that sodium bicarbonate which had the most distinct effect on gastric motility relieved the gastric distress of patients distinctly better than magnesium oxide or ventracon® regardless of the fact that the neutralizing properties of the administered ventracon® dose were as great and those of the magnesium oxide dose two or three times as great as those of sodium bicarbonate It also appeared that the therapeutic effect of these antacids was independent of the patient s having achlorhydria or an acid gastric secretion Why one patient obtains more relief from one drug than from another is not known

Pyloric Obstruction More Accurately Demonstrated by Food Barium Mixture Vincent W Archer and George Cooper Jr[6] (Univ of Virginia) studied gastric emptying time in 30 students after water barium and food barium meals With water barium meal 26 showed

[6] Roe tg 1 60 593 599 N mb 1949





F g 102 (t p) —\ x b w te b m t t p t t w th l g t d g d d l ul f b t t ympt m

F g 103 (bott m) —S m p t t La ge h fo l b m te t (Cou tesy f A h r \ \\ d Coope G J Am I Roentgen l 60 593 599 \

no six hour residue 2 showed only a trace and the others 5 and 10 per cent residue With food barium meal 18 showed no six hour residue 9 less than 5 per cent 1 10 per cent and 2 more than 10 per cent

In seven food barium meal caused no delay in stomach emptying as compared with water barium meal Food barium meal caused insignificant delay in 12 and moderate delay in 10 There was a large gastric food barium residue at six hours in one student whose stomach emptied a water barium mixture in six hours Only an occasional subject without gastric or duodenal pathology showed marked increase in six hour gastric retention after food barium as compared with water barium

When there is clinical evidence of obstruction and the question of surgical intervention arises comparison of obstruction to normal diet and to barium water mixture may be valuable as it was in the following case

Woman 53 had a long history of duodenal ulcer Pylorectomy and gastroduodenostomy had been done three years before but were followed two years later by return of symptom With water barium no six hour residue was seen by x ray (Fig 102) At six hours nearly half a food barium meal was still in the stomach (Fig 103) Subtotal gastric resection was followed by 4/ years freedom from gastric distress

Because vagotomy abolishes peristalsis it should be combined with gastroenterostomy when there is significant six hour barium food retention preoperatively

[Although gastric retention and pyloric obstruction are not synonymous terms the fact remains that there may be frank pa t or present clinical evidence of delayed emptying from whatever cause which frequently is not confirmed by the routine roentgenoscopic examination or even the six hour barium motor meal Hence the necessity of checking with food motor meal In view of such discrepancy the authors proposed combination of food and barium is logical and gives promise of possibly solving this particular problem —Ed]

Use of Antispasmodics and Spasmodics in Treatment of Gastrointestinal Disorders According to Philip Kramer and Franz J Ingelfinger[7] (Boston Univ) antispasmodics may affect gastrointestinal motor function by

(7) M Cl N th Am 91 1 71 45 S pt mb 1948

directly depressing smooth muscle activity opposing the action of the parasympathetic nervous system or imitating the action of the sympathetic nervous system In practice use of adrenergic drugs is disappointing because the side effects may be marked and action on the gastrointestinal motor function is often transient and insignificant Time and frequency of giving oral doses of antispasmodics should be determined by the chronological characteristics of the symptoms In general administration should be at stated times not as needed Antispasmodics act by substituting controlled intestinal motility for the abnormal motility causing the symptoms They will be of little value if used haphazardly or when the intestinal abnormality is at its maximum

Although the list of available antispasmodics is larger than ever before the authors recommend atropine levorotatory hyoscyamine (bellafoline®) and belladonna as the most effective depressors of intestinal motility As a general rule no more than 1 3 cc tincture of belladonna 0 6 mg atropine sulfate or 0 5 mg bellafoline® should be given at a single dose nor should more than four such doses be given within any 24 hour period Use of belladonna alkaloids and related substances is contraindicated if the patient is sensitive to them or has glaucoma Although scopolamine possesses well defined antispasmodic properties its routine use is not advisable as side reactions are often extreme and unpredictable Of the synthetic antispasmodics trasentine® and syntropan® may be used when belladonna alkaloids are contraindicated when gastroduodenal complaints are associated with irritation of the gastric mucosa and for colonic disorders Available evidence does not support the use of combinations of antispasmodics Inclusion of barbiturates is more frequently warranted because the sedative may allay neurogenic impulses that promote disorders of gastrointestinal motility

Spasmogenic drugs may increase intestinal motility by directly stimulating the muscle cell stimulating cholinergic activity or potentiating cholinergic activity

Drugs of this type exhibit anticholinesterase activity Cholinergic compounds consist of acetylcholine and its various substitutes Because of their untoward side effects and toxic reactions mecholyl® and doryl® are not recommended for use as spasmodics Although urecholine® is not generally available it appears to offer the greatest promise for clinical use It produces a clearcut increase in peristalsis and tone with minimal cardiovascular effects Its greatest use is in treatment of gastric retention after vagotomy for peptic ulcer Its action becomes apparent within 5 20 minutes of its subcutaneous admini tration and persists 30 60 minutes The undesirable effects of acetylcholine substitutes except doryl® can be counteracted by injection of atropine sulfate 0 6 mg subcutaneously In general patients with asthma should not be given cholinergic drugs

[On the basis of clinical and experimental observations Alvarez raises a dissenting voice in an editorial entitled Are Antispasmodics of Much Value? (Gastroenterology 12 155 January 1949) He claims that the gastrointestinal disturbances may not actually be the result of spasm or neuromuscular irritability and that many of the antispa modics recommended especially the proprietary ones are either ineffectual or of brief duration and frequently have unpleasant side effects —Ed]

Simple Nonirritating Tube for Feeding Purposes The modified Woldman tube described by William W L Glenn[8] (Jefferson Med College) is easily inserted into either stomach or upper small bowel and no obstruction of lumen due to twisting has been observed

APPARATUS —One end of a new Latex rubber Penrose drain 36 in long and ¼ in in diameter is securely tied with four strands of no 30 cotton thread looped twice around the tube (Fig 104) About 1 5 cc mercury is spilled into the open upper end and a second tie placed at the upper end of the mercury column Just above the mercury containing segment two or three generou sized holes are cut in the tube

METHOD —After the tube is well lubricated with mineral oil the patient s head and neck are extended and the mercury containing segment directed along the floor of the nose until the end reaches the pharynx The head is then flexed and the patient asked to swallow tubing outside the nose being held between the fingers while the tube is allowed to descend

(8) Gastroenterology 12 251 February 1949

slowly If the nose is deformed and passage of the tube not facilitated by a gentle push with a cotton tipped applicator the tube can be taken by mouth and its proximal end drawn into the nose after it has been tied to a small catheter inserted through a nostril into the throat Before feeding it is best to instill 10 cc sterile saline or water into the tube to ascertain that it is not in the trachea Tubes should be changed after 15 days

The tube has been used successfully for long periods in supplementary feeding of malnourished patients It has been used to bypass a poorly functioning stomach after vagotomy and has been passed into the distal jejunal loop at time of gastroenterostomy making jejunal

METALLIC MERCURY
1½ cc
ADAPTOR
diameter ⅝ inch
PENROSE TUBING
diameter ⅛ inch
holes cut in tube
COTTON THREAD

Fig 104 —Simple non-irritating feeding tube (Courtesy of Glenn W W L Gastroenterology 12 248 51 February 1949)

feedings possible in the event of a malfunctioning stoma A Levin tube for gastric suction may be passed through the same nostril Nose or throat irritation has not resulted from use of this tube

New, Safe, Simple Apparatus for Obtaining Negative Suction for Patient with Indwelling Gastrointestinal Tube K. Alvin Merendino and John A Phelan[9] (Univ of Minnesota) describe an apparatus which overcomes numerous disadvantages associated with three bottle suction sets

APPARATUS —The apparatus is a 14 gauge welded steel hollow tank with crown top and inverted bottom supported by four Faultless casters It weighs 40 lb The cylinder is 15¾ in in diameter and 24 in high In the crown top is a suitable handle for moving the piece a negative pressure gauge graduated in inches of mercury and a single orifice needle valve On the opposite side from the handle and recessed into the cylinder is a hand pump assembly which can be removed readily in case attention is necessary Removal of the pump

(9) Surgery 25 5 6 579 April 1949

assembly afford a 2 in opening for washing and emptying the interior of the cylinder The apparatus is connected to a catch bottle (Fig 105) which is in turn connected to the patient s gastrointe tinal tube

With needle valve closed 25 30 light slow strokes of the pump handle evacuate the tank and the gauge shows approxi mately 5 in negative mercury pressure After the nasal tube

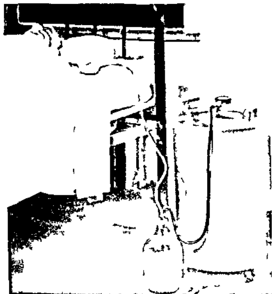


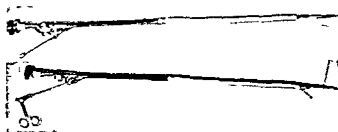
Fig 105 —S ct pp t Lrw mod l J H wh h b pl d d b d f g dd t on l p d g p t t b l (Cou y f M d K A d Ph l J A S g y 5 576 579 Ap l 1949)

is connected to the catch bottle the needle valve is opened The quantity of negative pressure is sufficient to drain about 4 gal liquid and/or air from the patient and suction to the drainage bottle and the patient need never be interrupted

Because the device is foolproof its chief advantage to the patient is safety It is impossible to create a positive pressure and because of absence of water in the system the patient cannot be flooded Bedside care of the appli ance ble saving valuable time for nurses The

expense of maintenance replacement washing and storage of bottles and tubing which is necessary with three bottle sets is practically nonexistent Potential sources of leak are reduced to a minimum Maintenance of the three pieces incorporated in the apparatus is simplified by use of easily obtainable standard parts

Operating Gastroscope To facilitate diagnosis in gastric disease Edward B Benedict[1] (Massachusetts Gen l Hosp) added an additional channel to the Schindler flexible gastroscope through which a plastic suction tube is introduced for aspirating secretions (Fig 106) After re



Fg 106 (t p) Fg 107 (bott m)
(Co t sy f B n dct F B Ga t t l gy 11 81 83 S ptemb 1948)

moving the aspirating tube the biopsy forceps is passed through the same channel (Fig 107) The instrument is provided with an adjustable eyepiece for fine focusing and a double thumbscrew for raising or lowering an elevator designed to aid in directing the biopsy forceps

Though experience with this instrument has not been extensive it has been passed without difficulty and satisfactory biopsies have been obtained with safety despite its slightly increased diameter

Description of New Gastroscope The instrument (Fig 108) described by Donald T Chamberlin (Boston) has a rigid section 51 cm long and provides improved definition larger image and better lighting The usual rubber finger like tip on the bulb has been replaced

(1) G t oe t l gy 11 281 283 S pt mbe 1948
( ) Ib d 12 09 211 Febr y 1949

by a smooth metal tip which makes passage easier without increasing risk of perforation A small wheel near the eyepiece raises or lowers the tip of the instrument when in place The lens may be brought away from the posterior wall in order to examine it more adequately and a retrograde view may be obtained without having a movable mirror in the lens The blind area between angulus and pylorus is greatly diminished since by depressing the tip one can get a further view beneath the angulus Increasing the length of the rigid portion and decreasing that of the flexible portion has made possible

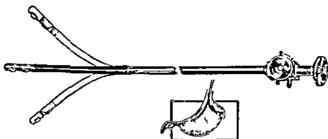


Fig 108—N w g t p (C rt y f Ch mbe l D T G t oe t l gy 12 209 211 F bru ry 1949)

installation of a more adequate optic system The angle of vision is 40 degrees the objective head may be elevated or depressed 30 degrees and an area 37 mm in diameter is seen at a distance of 2 in With experience it is no more difficult to pass than standard instruments

Gastric Ulcer Frances H Smith and Sara M Jordan[3] (Lahey Clinic) present data on 600 cases in 59 (9 8 per cent) of which the ulcer was malignant Of the other 541 ulcers 330 were treated medically and proved benign by the clinical course and x ray findings and 211 were proved benign by pathologic examination after resection Indications for operation in the 211 cases included a diagnosis or suspicion of malignancy in 89 recurrence in 70 failure to heal in 21 and complications in 29 Ten

(3) G t oe te logy 11 575 597 N mb 1948

patients died before leaving the hospital but only five died as the direct result of operation Only one patient had what he considered a recurrence of preoperative symptoms

Comparison of benign and malignant groups showed that males were a little more than twice as prone to gastric ulcer as females but more than four times as prone to malignant ulcer Symptoms were disarmingly similar in benign and malignant cases Marked weight loss occurred three times more frequently in the benign group Anacidity occurred almost twice as frequently in the malignant group but hyperacidity is not incompatible with gastric malignancy Incidence of hemorrhage obstruction and x ray deformity of the duodenum was comparable in both groups Perforation occurred twice as often in benign cases Hour glass deformity was preponderant in the malignant group Night pain was more common in malignant cases and nausea more frequent in benign cases

In differential diagnosis x ray study is the most valuable aid The importance of careful fluoroscopic and film examination cannot be overestimated Gastroscopy must be regarded only as an accessory to x ray study

Ulcers of the greater curvature and fundus had the highest percentages of malignancy 60 and 50 per cent respectively The prepylorus pylorus and corpus showed an incidence of malignancy of 17 per cent in each location The greater frequency of ulcers in the latter regions diminishes the percentile incidence but does not change the fact that the greatest number of malignancies are to be found in these areas

Of 111 patients followed 5 23 years only 2 died of recurrence with malignancy If to these are added the four patients who died of unknown cause (assumed to be malignancy) the percentage of deaths from cancer of the stomach is still only 5 4 Although gastric ulcer is potentially a site of malignancy the lesion is not so perilous that patients cannot be treated individually rather than by a general policy of resection

Gastric ulcers that fail to heal completely within six to eight weeks and all recurrent ulcers should be resected as soon as possible The criteria for healing are complete disappearance of the x ray defect complete subsidence of symptoms and disappearance and non recurrence of occult blood in the stool The patient should be impressed with the importance of complete co operation for maintenance of healing and immediate return for examination in case symptoms recur

[An instructive report which should be read in its entirety by those especially interested In opening discussion of this paper when presented before the Society I summarized those symptoms and signs which we have found useful in differentiating benign and carcinomatous ulcer I also called attention to the rarity of co existence of an active duodenal ulcer and gastric carcinoma in its small circumscribed form in our experience The authors emphasis on the sinister implication of the early recurrence of a gastric lesion following adequate medical treatment is a timely admonition if not actually an original and noteworthy observation —Ed]

Acute Duodenal Ulcer, according to Maurice Feldman[4] (Baltimore) occurs frequently in young adults and is often misdiagnosed because it does not present the characteristic picture associated with chronic duodenal ulceration Patients with acute duodenal ulcers usually have upper abdominal pain but often without relation to food or pain may be accentuated instead of relieved by eating Vomiting is common In most cases onset is abrupt with nausea vomiting pain and diarrhea X rays are usually not made because the patients are thought to have food poisoning indigestion or abdominal grippe The symptoms disappear spontaneously in a few days or a week in some patients with healing of the ulcer but most lesions progress to chronic ulceration

Diagnosis of duodenal ulcer is usually based on chronic anatomic deformity of the duodenal bulb Roentgen signs of acute early duodenal ulcer are localized edema swelling of the mucosal folds dilatation of the bulb with atony (Fig 109) whitewashed appearance of the bulb nonretentive irritable bulb fragmentation of the bulb and ulcer niche Secondary signs are edema of

(4) R Ga t oe t l 15 757 761 O t be 1948

the pyloric sphincter small gastric residue prominence *of mucosal folds along the greater curvature* of the stomach excessive gastric secretion and excessive air in the stomach In the early stages of duodenal ulceration the niche is not present but in the region of the ulcer a small rounded edematous swelling may be seen



Fig 109—D l ted ton bulb w th ul h d f ct at r w (C rt y f F ldman M R v G t t 1 15 75 761 O t b r 1948)

Though an ulcer crater was demonstrated in 36 2 per cent of 1 154 cases of duodenal ulceration at all stages the niche was found in only 20 per cent of 227 cases of acute duodenal ulcer

Duodenal Ulcer Follow Up Study of 305 Veterans Discharged because of Ulcer Allen E Hussar[5] (Los Angeles) points out that duodenal ulcer among military personnel was much discussed in the literature

(5) G str nt logy 11 183 197 A gu t 1948

during World War II because of its incidence difficul ties encountered in establishing diagnosis and the prob lem of finding the proper policy for disposition of af fected soldiers Because veterans receive disability com pensation if the ulcer was initiated or aggravated by military service a postwar problem has arisen namely the fate of duodenal ulcer in patients who are being compensated for their illness

Hussar interviewed and re examined 305 veterans to adjust their compensation received from the government according to status of their ulcer and degree of disabil ity Average length of time elapsed since separation from military service was 34 months Five patients had undergone surgery 300 had had medical management

X ray examination revealed an ulcer crater in 22 per cent irritable bulb in 11 per cent deformed bulb in 41 per cent and negative findings in 26 per cent Clinical activity as determined from the patient s symptoms was found in 60 per cent From combined x ray findings and symptoms ulcer was diagnosed as active in 68 per cent and inactive in 32 per cent Histories revealed that since separation from service 6 per cent had had no recur rences 9 per cent no symptoms if they adhered to their diet and 12 per cent rare 30 per cent frequent and 43 per cent almost continuous symptoms Thirty eight per cent of patients who had followed an adequate or fairly adequate ulcer regimen had frequent recurrences or con tinuous symptoms and were therefore classified as in tractable to medical management

The figures for this group of patients indicate that rates of activity recurrences and intractability were higher than could have been expected from previous ex perience High activity of ulcers was attributed to two principal factors compensation and incorrect ulcer life and unsatisfactory management of recurrences Receipt of compensation appeared to have exaggerated symp toms and interfered with healing through a psychoso matic pattern Improper ulcer management also played a role over half the patients had not consulted a physi

cian since discharge from service used alcohol freely smoked heavily and failed to follow proper dietary rules

Hussar recommends that the compensation factor be eliminated by assuring the veteran with duodenal ulcer that he will receive compensation throughout his life regardless of the status of his ulcer that proper education in ulcer management be given such patients and that psychotherapy be made available to them

Analysis of X Ray Findings in 405 Cases of Benign Gastric and Pyloric Ulcer Walter A Russell Sydney Weintraub and Harold L Temple[6] (New York Hosp) make a plea for standardization of anatomic terminology with reference to the stomach and offer their suggestions (Fig 110) Analysis of 429 ulcers (405 patients) showed 278 (64 8 per cent) in the pars media and incisura angularis mostly along the posterior wall of the lesser curvature There were 81 (18 9 per cent) pyloric and 35 (8 2 per cent) prepyloric ulcers The following criteria were accepted for diagnosis of pyloric ulcer lengthening of the pyloric sphincter (wide interval) distortion of the sphincter (crooked stem) a niche usually small in the elongated canal There were 2 ulcers in the fundus 1 in the greater curvature and the remaining 32 ulcers (7 5 per cent) in the portion of the antrum proximal to the prepyloric area

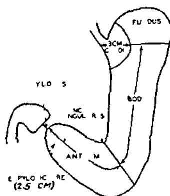


Fig 110—Proposed anatomic terminology applied to the entire stomach (Courtesy of Russell W A et al Radiology 51 790 797 December 1948)

There is frequently a discrepancy between the roentgen location of a lesion and that reported by a surgeon and occasionally by the pathologist This usually occurs

(6) Radiology 51 790 797 December 1948

in the pyloric region The radiologist can be more accurate because during examination a distinct dividing line between stomach and duodenum is produced by the pyloric sphincter When anesthesia is given the pyloric muscle is relaxed and frequently cannot be palpated thus making it difficult for the surgeon to use it as a landmark for locating the ulcer Since the course of the pyloric vein frequently is anomalous it is of little use as a guide to the surgeon

Medical treatment gave good results in 44 8 per cent of 145 patients so treated Of 151 treated by gastric resection results were good in 92 1 per cent Other types of operations in 56 patients resulted in 62 5 per cent good results Of the ulcers measured 275 were under 2 5 cm in diameter and 35 were of that size or larger Of the larger ulcers 26 were proved benign after resection and 5 after a medical follow up of five years or more Ratio of males to females was 2 7 1 Peak for age incidence for all patients was the fifth decade and 85 9 per cent of all patients were 40 or over Multiple gastric ulcers were observed in 23 cases

There was a definite diagnostic error of 8 8 per cent in 371 x ray examinations In 22 cases (5 9 per cent) the lesions were called malignant and in the others the lesions were not identified or located although in some a diagnosis of pyloric obstruction was made

Factors Influencing Mortality from Acute Perforated Peptic Ulcers William T McElhinney and Charles E Holzer Jr [7] (Cincinnati Gen l Hosp) report that the operative mortality in 336 cases of acute perforated peptic ulcer seen between 1935 and 1946 was reduced from 21 per cent in the first three years to 10 7 per cent for 1944 46 One of the most important factors affecting operative mortality in such cases is the time elapsing before the perforation is closed In the most recent group of patients undergoing operation in the first 12 hours mortality dropped to 6 4 per cent Over three

(7) Surg Gynec & Obst 87 85 9 July 1948

times as many deaths occur in the 50 59 year age group as in the 20 29 year group

A history of previous epigastric distress was given by 87 per cent of the patients Vomiting occurred after perforation in 47 per cent White cell count was usually elevated Temperature on admission was less than 99 F in 53 per cent of the cases Free air was demonstrable roentgenographically in the peritoneal cavity in 66 per cent A boardlike or markedly spastic abdomen was noted in 68 per cent The perforation was duodenal in 56 8 per cent and pyloric in 27 9 per cent

In 13 cases diagnosis was not made on admission The ulcer had been perforated more than 24 hours in 12 One of the causes for delay in diagnosis was gradual onset

Three adjuvants to routine treatment are continuous gastric suction spinal anesthesia and chemotherapy All patients received adequate fluids preoperatively and antishock therapy In the group operated on within the first six hours after perforation and given penicillin and sulfadiazine mortality dropped to zero In those operated on within 7 12 hours after perforation and given chemotherapy mortality was 7 7 per cent Since the use of penicillin there have been no subphrenic abscesses, whereas with sulfonamide therapy alone or no chemotherapy 11 such complications developed Positive cultures were obtained at operation in 88 per cent of the fatal cases occurring in the last six years Since peritonitis was the greatest single cause of death the authors conclude that the bacterial element in perforated ulcer is important Streptococcus was identified in 75 per cent of the positive peritoneal cultures

Early diagnosis and prompt surgery with supportive chemotherapy are the most important factors in successful treatment of acute perforated peptic ulcer

Perforated Gastric and Duodenal Ulcers Analysis of 200 Consecutive Cases is reported by E Roderick Shipley and J H Walker[8] (Baltimore) There were 187

(8) Am J S g 77 3 9 337 M ch 1949

males The youngest patient was 19 and the oldest 76 Mortality increased with age but sex race and season were not of prognostic significance The majority (62 per cent) were laborers and not high strung nervous individuals in contradistinction to earlier observations A history of gastric disturbances was found in 89 per cent and 30 per cent had used alcohol during episodes of gastric upset or just before perforation

Diagnosis was correct in 95 5 per cent There was a fairly definite history of gastric or duodenal ulcer with exaggeration of symptoms a day or two before perfora tion sudden sharp epigastric pain nausea and prostra tion Vomiting was not constant and hematemesis was unusual Boardlike rigidity of the abdomen with extreme tenderness and muscle spasm leukocytosis quiet abdo men on auscultation and gradually rising temperature and pulse rate as peritonitis spread were noted Free air in the peritoneal cavity was seen by x ray in 60 4 per cent of 48 patients

The site was duodenal in 39 5 per cent pyloric in 15 per cent and gastric in 45 5 per cent There were three perforated malignant gastric lesions Simple single layer closure with omental graft has become the pre ferred procedure because of the mounting mortality rate and frequent complications associated with more complicated procedures

Postoperatively gastric suction is maintained 12-48 hours with sips of water after 12 hours Parenteral feed ings include adequate amounts of protein vitamins sa line and glucose Chemotherapeutic and antibiotic agents are used prophylactically to combat or prevent perito nitis wound infections and pneumonia

Over all mortality was 26 per cent or 20 per cent in the 188 who underwent operation Early surgery age correct diagnosis anesthesia surgical procedure co existing medical diseases complications and use of chemotherapeutic agents were important influences on mortality Commonest complications were wound infec

times as many deaths occur in the 50 59 year age group as in the 20 29 year group

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Perforated Gastric and Duodenal Ulcers Analysis of 200 Consecutive Cases is reported by E Roderick Shipley and J H Walker[8] (Baltimore) There were 187

(8) Am J Surg 77 3 9 33 Mar h 1949

The absence of free hydrochloric acid in the gastric contents after stimulation with histamine in the presence of a demonstrable gastric or duodenal lesion is justification for the routine exclusion of carcinoma lymphogranuloma, syphilis or tuberculosis Inconsistent in particular is the diagnosis of an active duodenal ulcer in the presence of histamine refractory achlorhydria Yet such spurious achlorhydria occasionally occurs after injection of an adequate amount of pharmacologically active histamine base (0 1 mg /10 kg body weight) and proper intubation procedure Why such misleading achlorhydria may occur even in the presence of an unhealed duodenal ulcer is still not clear Such cases have been classified as refractory or as instances of delayed secretion Schiff observed a complete cessation of secretion of hydrochloric acid in a laboratory worker over a period of two months the cause of which was not ascertained. Wolf and Wolff observed a similar phenomenon over a similar period in their subject with a gastric fistula and attributed it to emotional causes —Ed]

Effect of Insulin Hypoglycemia on Gastric Secretion in Duodenal Ulcer and Controls Previous studies have established that insulin hypoglycemia stimulates the dorsal vagus nucleus and that this vagal stimulation results in increased secretion of hydrochloric acid in the stomach Theoretical considerations suggest that the vagus nerves play an important role in genesis of peptic ulcer Asher Winkelstein and Manfred Hess[1] (New York City) conducted studies on 18 normal controls and 21 patients with duodenal ulcer to determine the role played by the dorsal vagus nucleus in gastric secretory disturbance of duodenal ulcer

Results showed that 15 units of insulin given intravenously evokes a markedly higher acid response in duodenal ulcer patients than in normal persons Average rise in free acidity was 43 units in controls and 77 units in ulcer patients Smaller doses of insulin (5 units intravenously) act similarly but the responses are less marked Subcutaneous administration of insulin was unreliable as a test for vagal gastric acid secretion

These results seem to give further support to the rationale of vagotomy in therapy of peptic ulcer whether used as a prophylactic measure against postoperative recurrence after subtotal gastrectomy or as a primary curative measure for duodenal ulcer Evidence suggests

(1) G t t l gy 11 326 334 S pt mbe 1948

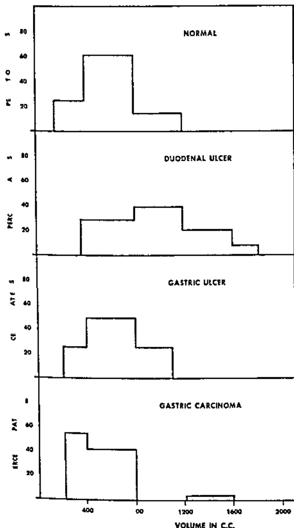
tion peritonitis and some pulmonary pathologic process The mortality rate for patients who had spinal anesthesia was 12 per cent in comparison with 21 per cent for those having general and 42 per cent for those having both types

Achlorhydria and Peptic Ulcer Further Study of Role of Peptic Activity in Pathogenesis and Course of Peptic Ulcer William E Ricketts Walter Lincoln Palmer Joseph B Kirsner and Anna Hamann[9] (Univ of Chicago) have found that the question of achlorhydria or even of a low secretory rate almost never arises in acute duodenal ulcer However gastric ulcer may occur not only without hyperacidity or hypersecretion but with very low concentrations of acid in terms of response to stimulation with histamine They observed the fortuitous development of complete achlorhydria in two patients with gastric ulcer followed for 10 years or longer One had a large chronic lesion that disappeared during 10 days of antacid therapy then recurrent small transitory ulcers at intervals until complete achlorhydria appeared Since then there has been no recurrence Low acid secretions were noted with 21 per cent of 170 gastric ulcers studied but not with active duodenal ulcer

The term peptic ulcer presupposes presence of hydrochloric acid Peptic activity occurs only in the acid range of pH the optimal point being 2.6 with activity decreasing to a pH of 5 Further evidence of the validity of the concept of peptic ulcer is provided by the invariable healing observed after appearance of spontaneous or induced achlorhydria lasting 90 days or longer by the high incidence of healing in phases of achlorhydria of less than 90 days duration and by failure of the ulcer to recur during achlorhydria The authors conclude that a simple means of producing achlorhydria would solve the ulcer problem

[This contribution is a fitting sequel to that of the earlier one by Palmer and Nutter (1940) on the subject of peptic ulcer and achlorhydria I should like to comment on the diagnostic aspect

(9) A n I t. M d 30 24 39 J ry 1949



Fg 111—D trb t on f t t l l m f l hou oct l g t t
(Cou t y f L E t l A h S g 56 345 356 M h 1948)

that it is probably of fundamental importance to control or allay the hyperirritability of the dorsal vagus nucleus in therapy of peptic ulcer

Nocturnal Gastric Secretion Studies on Normal Subjects and Patients with Duodenal Ulcer, Gastric Ulcer and Gastric Carcinoma Erwin Levin Joseph B Kirsner Walter Lincoln Palmer and Carrie Butler (Univ of Chicago) report that the volume of the 12 hour nocturnal gastric secretion (Fig 111) of 33 normal subjects ranged from 148 to 1 188 cc (average 581 cc) Average volume secreted by men was 643 cc and by women 460 cc Volume was below 800 cc in 86 per cent of the studies and below 600 cc in 50 per cent

In 74 studies on 32 patients with duodenal ulcer volume ranged from 362 to 1 839 cc (average 1 004 cc) It was below 800 cc in 32 per cent of the studies and in 47 per cent it was above 1 000 cc as compared with only 4 per cent in the normal group

In eight patients with gastric ulcer volume ranged from 202 to 1 122 cc (average 623 cc) It was below 800 cc in 75 per cent of the studies and below 600 cc in over 50 per cent

In 12 patients with gastric carcinoma volume ranged from 205 to 1 243 cc (average 436 cc) It was below 800 cc in 96 per cent of the studies and below 400 cc in over 50 per cent

The free acidity of the 12 hour nocturnal gastric secretion (Fig 112) in normal subjects ranged from 1 to 90 clinical units (average 29) There was no significant difference between men and women Free acidity was below 40 clinical units in 72 per cent of the studies and below 30 units in over 50 per cent In contrast only 20 per cent of the patients with duodenal ulcer had an acidity below 40 units whereas 60 units or more was found in 50 per cent values ranged from 13 to 112 units (average 61)

Acidity was below 40 clinical units in all patients with

(2) Arch Surg 56 345 356 March 1948

ent in 42 per cent of the carcinoma group in 33 per cent anacidity was persistent in all specimens on two consecutive nights Amount of free acid was below 10 units in 81 per cent of this group

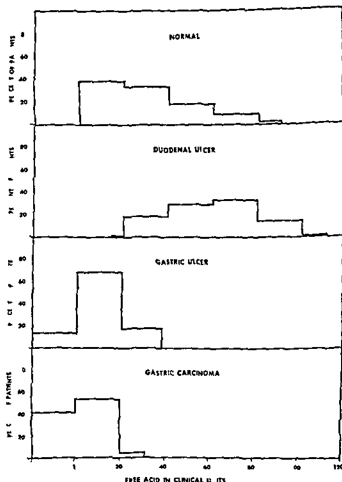
Thus the volume and output of hydrochloric acid are usually highest in patients with duodenal ulcer For a small series of patients with gastric ulcer average volume of gastric juice was about the same as for normal subjects but average content of hydrochloric acid was lower Nocturnal gastric secretion was lower in patients with gastric carcinoma than in normal subjects and in patients with gastric ulcer

Comparison of Nocturnal Gastric Secretion in Patients with Duodenal Ulcer and in Normal Individuals is presented by Erwin Levin Joseph B Kirsner Walter L Palmer and Carrie Butler[3] (Univ of Chicago) Continuous gastric aspiration from 8 30 p m to 8 30 a m was carried out on 32 patients with duodenal ulcer Total volume amount of free acid and total amount of free hydrochloric acid were averaged and these averages compared with results of a similar study on normal persons (Fig 113)

Secretion of acid gastric juice in patients with duodenal ulcer was continuous Volume concentration and acid output in the fasting nocturnal gastric secretion were higher in patients with duodenal ulcers than in normal persons Volume of secretion and acid output were usually higher during the first half than during the last half of the night Individual variations were found but patients with duodenal ulcer who had a high volume and a large amount of acid on one night usually showed similar findings on successive nights This was true also for patients with low secretory rates Rate of gastric secretion was not constant but varied spontaneously from hour to hour in the same person

Conclusions drawn from this study are the opposite of those presented in the only other published similar

(3) G t oe t l gy 10 95 964 J 1948



F g 11 —D t b t on f f hyd ochl r a d n 12 h t l g s tr c s r t (Co t y of Le n, E t l A ch S g 56 345 356 M r h 1948)

gastric ulcer and carcinoma Anacidity was observed in 13 per cent of the studies on the ulcer group although in none was it persistent when aspirations were repeated on successive nights In contrast achlorhydria was pres

It is suggested that the abnormalities detected in this study be taken into account in evaluation of preparations and procedures designed to reduce gastric secretion

Observations on Excessive Nocturnal Gastric Secretion in Patients with Duodenal Ulcer Joseph B Kirsner Erwin Levin and Walter Lincoln Palmer[4] (Univ of Chicago) report five cases in which nocturnal gastric secretion exceeded the mean for normal persons by four to seven times and surpassed the general average for patients with duodenal ulcer Clinical courses were characterized by severe pain and serious complications including hemorrhage perforation recurrent ulcers after partial gastrectomy and after vagotomy and gastrojejunocolic fistula Atropine in therapeutic doses up to 6 mg had no consistently significant effect in the four patients so treated This indicates that mechanisms other than or in addition to secretory hypertonus of the vagus nerves operate to maintain excessive production of hydrochloric acid

Large doses of enterogastrone® concentrate also failed to reduce nocturnal gastric secretion in the three patients so treated Irradiation of the fundus and body of the stomach effectively reduced gastric secretion with subsequent healing of the ulcer in one of four patients

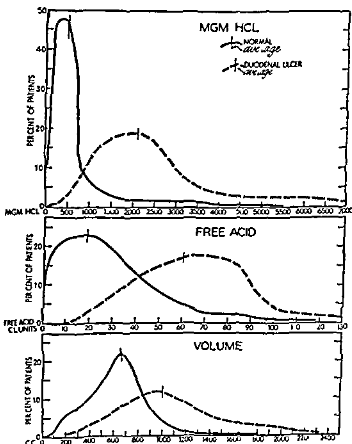
In two ca es vagotomy was followed by a pronounced decrease in the output of acid and by healing of the ulcer In two patients in whom vagotomy was incomplete gastric secretion was not permanently reduced and ulcers recurred In one of these marked hypersecretion had been present despite resection of three fourths of the stomach including the antrum

These findings emphasize the importance of acid gastric juice in the pathogenesis and persistence of peptic ulcer

[The results of these successive investigations on nocturnal gastr c secret on especially in patients with duodenal ulcer are in acco d with the large majority of other studies carried out both at home and abroad It is apparent that the average volume of

11 598 617 N mbe 1948

investigation This discrepancy results from the fact that in the previous investigation medical personnel were used as normal subjects Studies by the present



F g 113—D st but on of l m f a d ty d mou t of hyd ochl a d n 12 h r noctu l g t sec t on mal pe nd n p t ts w th d ode l ulcer (Co rt y f *Le E. r l G t oe te logy 10* 952 964 June 1948)

authors showed the highest values for stomach secretion in normal persons to have been among medical person nel

previous knowledge anent gastric secretory status in gastric ulcer These secretory findings of course have a definite bearing on treatment whether medical or surgical and prognosis particularly with respect to duodenal ulcer One is reminded of Drags edt s observation that the medical management of duodenal ulcer has been successful directly in proportion to the degree in which the acid gastric juice has been neutralized during the entire 24 hours —Ed]

Study of Gastric Mucosa in Various Diseases Affecting Upper Part of Gastrointestinal Tract Ward Carl Meyers[5] (Mayo Found) studied pathologic sections of gastric mucosa from 25 patients with duodenal ulcer 25 with gastric ulcer 25 with carcinoma of the stomach and free hydrochloric acid 25 with gastric carcinoma and achlorhydria and 35 with pernicious anemia

In pernicious anemia thickness of all layers of the gastric wall was diminished Thickness of mucosa and external muscular coat was of little consequence in the other conditions Length of the glands in ulcer and carcinoma with or without hydrochloric acid differed little There was less destruction of epithelial elements in duodenal ulcer than in gastric ulcer but destruction was uniform and slightly more severe in gastric cancer Except in the presence of overwhelming atrophic gastritis attempts at glandular regeneration were usually found Pinching off of glands by the muscularis mucosa (Fig 115) was taken as evidence of severe destructive gastritis with subsequent healing leaving blind glands buried in the mucosa

The number of parietal cells was high in duodenal ulcer and diminished in the other conditions Lymphocytic infiltration was greater in the antrum than in the fundus in duodenal ulcer and greater in the pylorus than in the fundus in gastric ulcer Slightly more infiltration was found in the pylorus in carcinoma Submucosal edema was common in all grades of gastritis Submucosal fibrosis was more common in severe atrophic gastritis Cellular infiltration of the submucosa was more extensive in carcinoma and pernicious anemia than in

(5) G t oe t logy 10 9 3 938 7 1948

gastric secretion and the average output of hydrochloric acid are highest in patients with duodenal ulcer That there is no signifi cant difference in the average volume secreted by patients with

NOCTURNAL GASTRIC SECRETION(HCL MG) AND COURSE OF PEPTIC ULCER

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F g 114—N t n l g t c s t n a d f d od n l I of fi ye s du t n m 43 (C t y f K n J B t t G st o- e t l gy 11 598 617 N mb 1948)

benign gastric ulcer and normal individuals and that the concen tration and output of free hydrochloric acid are actually somewhat lower in patients with gastric ulcer is no surprise light of

tain the anatomic and physiologic state of the residual stomach gastroenterostomy stoma and adjacent jejunum

Gastroscopy was done on 17 patients 9 21 days after operation Abnormalities were seen in 10 In eight the most constant finding was edema and/or erythema usually localized at or adjacent to the stoma No relation could be established between hypoproteinemia and edema noted gastroscopically Only 2 of the 17 had



Fig 116—Appe g t p m t 5 4 m th tte bt tal g t e tomy w th t g t my n m l t m d ff th k g nd dem f d j g t po h d l t ly l d j j m (Courtesy f Pa lson M J Gladd d E S Ga t oent logy 10 970 977 J 1948)

gastrointestinal complaints aside from the usual postoperative distress One of these had 24 hour barium retention and in the other gastroscopy revealed superficial gastritis

Gastroscopic examination was done on 21 patients longer than *three weeks postoperatively (Some of these* were also studied in the immediate postoperative period) Five had constant and six inconstant abnormalities consisting of erythema edema thickening and encroach*ment on the stoma* or several of these abnormalities *In* one patient gastroscopy 5½ months after subtotal gas

ulcer Changes in the muscularis were most common in pernicious anemia of intermediate degree in cancer and least in ulcer There was little difference in the degree of gastritis noted in carcinoma with and without hydrochloric acid

Meyers believes that gastritis begins with hyperemia and cellular infiltration When chronicity occurs the



Fig 115—Se t n of m c l s m co a w th wid ly pl t t nds and occa n l pinch g ff f gl nd F ee str nds e t nd pwa d towa d l me H mat xyl n and o n ed d f m × 42 (Court y of Meyer W C. G t te l gy 10 923 938 J 1948)

mucous membrane passes through successive stages of glandular destruction erosion cyst formation destruction of the muscularis and finally complete atrophy Simultaneously there are sporadic attempts at gland regeneration

Partial Gastrectomy Clinical, Gastroscopic and Radiologic Considerations Moses Paulson and Eugene S Gladsden[6] (Johns Hopkins Univ) performed gastroscopy on 25 patients after subtotal gastric resection to ascer

(6) Gastroent rol gy 10 970 977 J ne 1948

functions well protects the gastric mucosa from traumatic factors by permitting more rapid gastric emptying and by permitting reflux of alkaline bowel contents The rapid gastric emptying accounts for the relatively smaller incidence of gastritic changes in cases in which gastroenterostomy was done at the time of vagotomy

[It is reasonable to predict that further studies of this nature some of which have already been published will enlighten us with respect to the secretory motor and mucosal abnormalities following bilateral vagotomy Current reports are not too encouraging to the proponents of this procedure in this re pect Of interest is the prophylactic or ameliorating effect of a properly functioning gastroenterostomy —Ed]

Gastroscopic Appearances Following Vagotomy Significance of Observations in Relation to Gastric Innervation Moses Paulson and Eugene S Gladsden[8] (Johns



F g 117 (l ft) —Appe m h fte t g f p f ted d o d l l d t th g tomy I l t t w g t R t t p talu na t ty d p tul f trum d pyl w p se t A trum cov m t f pyl pb ct
F g 118 (e t) —Appea ce on y fte turi g f perf t d d o den l lc d t b ci gotomy I l t t w po t U su l occu f d d d p talt ct ty f t m d pyl ph nct
F g 119 (ght) —Appea ce sev n month ft tu g f pe f ted l d t h ci g tomy I sub t t w gati U l p t f peri t lt nact ty d pat lou t f pylorus.
(C rtesy of P l M d Gladsd E. S J A. M A 139 151 152 Ja 15 1949)

Hopkins Univ) report gastroscopic studies during the first postoperative year on 24 peptic ulcer patients In the 10 with vagotomy alone the stomach was large and atonic and mucosa of normal color There was little evidence of peristaltic activity The pylorus was patulous and continually open (Figs 117 and 119) Within the

(8) J A M A 139 151 15 J 15 1949

trectomy showed a normal stoma and jejunum but diffuse thickening and edema of the residual gastric pouch (Fig 116) Blood protein examinations were not done often enough in this group to permit correlation with gastroscopic appearance Roentgen examination rarely revealed any anatomic or functional change

Gastric Mucosa after Vagotomy for Peptic Ulcer To evaluate further the effect of vagotomy on gastric mucosa Leonard M Asher (Los Angeles) studied 20 patients gastroscopically On 8 of these patients transthoracic vagotomy alone had been done and on the other 12 vagotomy and either pyloroplasty or gastroenterostomy for refractory duodenal ulceration

Definite abnormalities of the gastric mucosa were observed in 15 patients The mucosal changes most commonly seen consisted of hypertrophic gastritis not limited to any one portion of the stomach and frequently associated with superficial erosions These changes occurred in six patients having vagotomy alone and in five on whom gastroenterostomy was done at the time of vagotomy Four patients had only minor changes in the gastric mucosa and five had normal mucosa

Changes occurring as a result of vagotomy are thought to influence development of gastritis These changes consist of altered circulation altered secretion of mucin together with dissociation of acid and mucin secretion and altered motility It is hypothecated that these changes reduce resistance of gastric mucosa to physical trauma

It was impossible to correlate changes seen in gastric mucosa with degree of free acidity found after vagotomy Nor could mucosal changes in patients with gastroenterostomy be correlated with results of the insulin test In patients who had vagotomy alone gastritic changes developed despite the fact that the insulin test indicated that vagotomy had been complete

The author suggests that a gastroenterostomy which

(7) Gastroenterology 11 393 317 September 1

la ting 20 minutes Fresh juice was prepared twice daily A mixture of 75 per cent cabbage juice and 25 per cent fresh celery juice (stalk and greens) wa more palatable Chilled juice was given patients in 200 cc amounts five times a day

X rays showed that the average healing time for seven patients with duodenal ulcer treated with cabbage juice was 10 4 days compared with 37 days in cases reported in the literature Average healing time for six patients with gastric ulcer including one with marginal ulcers was 7 3 days compared with 42 days in cases from the literature Gastroscopic examination confirmed x ray findings

The results of fresh cabbage juice therapy are not adequate proof that cabbage contains an unidentified factor (vitamin U) which apparently plays a specific role in healing peptic ulcers This factor is present in varying concentration in many fresh greens cereal grasses fresh milk raw egg yolks certain animal and vegetable fats and gastric mucosa It has not been identified as one of the known vitamins or food factors Preparation of food by heating or cooking may completely destroy this substance No extract or concentrate containing vitamin U has been developed for clinical trial

[Recent measures advocated for treatment range from pituitary snuff to fresh cabbage juice! To the e can be added mucin protein hydrolysates amino acids resins certain detergents and what have you No doubt all of these have their virtues to more or less degree as remedial agents because of their buffering protecting neutralizing or nutritive effect However they hould be regarded more as ancillary to conventional or standard methods of treatment whenever indicated —Ed]

Prevention of Recurrences in Peptic Ulcer Theodore L Althausen[1] (Univ of California) is convinced that the peptic ulcer problem would be greatly lessened if attention were directed to prevention of recurrences The most important known causes of ulcer recurrences are physical and mental fatigue emotional disturbances dietary indiscretions and infections

Prevention of recurrence should start before treatment with careful diagnosis Correlation of x ray findings with

(1) A I t M d 30 544 559 M h 1949

first year a tendency to restoration of normal tone and peristalsis was noted (Fig 118)

Similar changes were noted in the five patients treated by vagotomy and gastroenterostomy The stomal openings tend to be more patulous and less active than with gastroenterostomy without vagotomy Superficial erythema of the mucosa was present

In the residual gastric pouch of all nine patients treated by vagotomy and subtotal gastric resection erythema thickness and occasional edema of the mucosa were present The stomal openings were larger than is usually seen with subtotal gastrectomy alone Since the mucosal changes were similar to those found after subtotal gastric resection without vagotomy severing of the nerves does not protect against postoperative gastritis

The finding of an open pylorus suggests that gastric emptying may be more dependent on gastric tone and peristalsis than on pyloric tonicity when bilateral vagus section has been performed

Rapid Healing of Peptic Ulcers in Patients Receiving Fresh Cabbage Juice Garnett Cheney[9] (Stanford Univ) treated seven patients with duodenal ulcer five with gastric ulcer and one with gastrojejunal ulcers with fresh cabbage juice because experiments indicate that it contains an anti peptic ulcer factor Patients were closely followed by x ray examination kept in bed until pain ceased and permitted to smoke as many cigarets as desired but were forbidden alcoholic beverages All fresh and uncooked *foods* were *eliminated* and patients were served heated food only to eliminate possible food sources of the anti peptic ulcer factor All were required to take at least 1 liter of fresh cabbage juice daily

METHOD—Cabbage heads were not selected but only green cabbage was used although it was paler in the fall than in spring and summer All of the cabbage head was used A juice press was used to obtain clear juice About 2 kg cabbage was fed into the press to obtain 1 000 cc juice in an operation

(9) California Med 70 10 15 January 1949

stages of ulcer regimen or soon after cessation of treat ment in absence of known causes of recurrences Patients who show hyposensitivity to pain are particularly diffi cult to handle They should have a strict and prolonged course of ulcer therapy with frequent stool examination for occult blood and periodic x ray checks

There are no proved specific preventive measures for peptic ulcer although enterogastrone * thought to act by building up mucosal resistance to ulceration has shown promise in prevention of recurrence While the patient is still under active treatment general measures for prevention should be started In understandable lan guage the patient should be informed that the cause of peptic ulcer is unknown but that recurrence is due to constitutional predisposition in conjunction with certain unfavorable environmental factors To avoid his receiv ing a distorted view from unreliable sources the common ulcer complications should be described and reassurance given that duodenal ulcers do not become cancerous Sig nificance of insidious onset of vomiting or appearance of digested blood in stools should be stressed The phy sician should inform himself in detail about the patient s occupational and home environments and make construc tive suggestions on ways to lighten burdens they may impose Importance of proper relaxation and vacation periods should be stressed The typical ulcer patient is a tense ambitious meticulous overconscientious person who minimizes pain and neglects treatment because it in terferes with work Proper education in essentials of the ulcer problem overcome this attitude and change it to meticulous observance of the immediate therapeutic regi men and the long range program of prophylactic mea sures

Although details and strictness of dietary precautions depend on the physician s judgment he should impress every patient with the importance of moderation in eat ing (especially meats) of omitting chemically irritating coarse or excessively hot or cold foods of chewing foods thoroughly and of adhering to a regular meal schedule

clinical history the patient s psychic make up and physical examination especially the presence of sharply circumscribed tenderness over the duodenum is important Functional indigestion of undetermined origin should never be diagnosed as ulcer

The second preventive step is adequate treatment During the first week diet is limited to milk and cream mixture given every hour or two alternating with antacids Antispasmodics are always given and a sedative prescribed three times daily During the second week this schedule is continued and certain bland foods added if complete freedom from pain was achieved in the first period Eggs cottage cheese white bread oatmeal Cream of Wheat macaroni potatoes rice sugar salt and butter are acceptable additions Great emphasis should be placed on regularity of food intake and antacid administration during the first two treatment periods Usually cooked fruits and pureed vegetables may be added at the beginning of the third week and strict punctuality of schedule relaxed Thereafter gradual additions are made with less frequent administration of milk and antacids until the patient is on a general diet with certain long range precautions three months after beginning of treatment Antispasmodics should be used at least four months antacids at least six months and sedatives as indicated The physician s judgment of the individual patient indicates whether hospitalization is used during the first two or three weeks treatment

So called intractable cases may be due to the patient s lack of co-operation or the physician s failure to take full advantage of standard therapeutic measures Compromising the diet outlined increases the number of patients who fail to respond to medical therapy and inadequate treatment may result in partial or complete loss of pain while ulcer activity continues If the physician is satisfied with anything short of complete cessation of epigastric discomfort many patients neglect the regimen The most reliable indication of low grade activity in ulcers under treatment is return of pain during later

stages of ulcer regimen or soon after cessation of treatment in absence of known causes of recurrences Patients who show hyposensitivity to pain are particularly difficult to handle They should have a strict and prolonged course of ulcer therapy with frequent stool examination for occult blood and periodic x ray checks

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all for many years Because they increase gastric acidity and sensitize gastric secretory mechanism to other secretory stimulants all caffeine beverages and alcohol should be avoided Smoking should also be forbidden but because of its much firmer grip on most patients the physician must evaluate whether the restlessness and distress which accompanies such cessation may not overbalance advantages to be gained by abstinence Benzedrine or thyroid in the absence of hypothyroidism should not be used to combat fatigue Various infections especially of the upper respiratory tract initiate recurrences and patients should be impressed with the importance of guarding against them

In outlining a long range program for prevention of recurrences physicians should allow patients every leeway justifiable in the individual case lest by insisting on measures excessively strict from the patient s viewpoint the latter be prejudiced against the whole preventive program Each patient should be prepared to handle any recurrence of pain suggesting ulcer by going promptly on the first stage of strict ulcer diet and reporting at once to his physician

True ulcer intractability on a strict medical regimen in a hospital frequent disabling recurrence despite adequate prophylaxis and inability or unwillingness to follow such a regimen are indications for surgical intervention Subtotal gastrectomy or vagotomy done by experts results in improvement for most patients if performed for valid indications

[A number of contributions in recent years of similar nature attest the importance of this phase of ulcer treatment, one which has not been stressed sufficiently in the past.—Ed.]

Management of Gastric Hemorrhage, Using Topical Thrombin. The commonest complication of peptic ulcer is hemorrhage Severe bleeding is more common in persons over 40 because of rigidity of the arterial walls Mortality in this age group is eight times that of persons under 40 Mortality of persons whose hemoglobin level is below 9 4 Gm (60 per cent) is four times that of persons with a level above 60 per cent

Thrombin is a sterile standardized hemostatic powder obtained from bovine plasma and supplied in sterile packages of ampules containing 5 000 Iowa units Its action depends on its ability to clot fibrinogen T M Rogers (Sterling Colo) reports two cases of gastric hemorrhage in which dramatic response followed oral administration of topical thrombin The first patient was a man 64 with severe gastric hemorrhage due to erosion of peptic ulcer into a large blood vessel The second case is reported here

Boy 16 wa hospitalized after a large bloody emesis two hours previously On admission he vomited about 2 cupfuls of dark brown blood Three weeks previously rheumatic fever was diagnosed and large doses of acetylsalicylic acid were given For three days before admission rather indefinite symptoms of gastric distress occurred about two hours after meals Examination revealed a rapid thready pulse and a mild systolic murmur at the apex and in the left axillary region There was definite midepigastric tenderness Blood count revealed 3 050 000 red cells 11 000 white cells and hemoglobin level 9 4 Gm Thrombin 10 000 units in an isotonic solution was given orally that evening and repeated three times next day A modified Andresen diet was given Recovery was prompt and uneventful and the boy was discharged 12 days later on a modified ulcer diet Follow up three months later revealed no recurrence of bleeding or gastric distress Enteric coated salicylates are being administered

[Rogers is more optimistic of the efficacy of such a hematinic especially when orally administered than I am The same goes for thromboplastin the proprietary koagamin® even when administered parenterally However I am agreeable to remain open minded about it Thrombin has also been advocated following liver therapy puncture (Lancet 1 523 Mar 26 1949) In these circumstances it is injected into the needle track —Ed]

Hematemesis with Special Reference to Chronic Peptic Ulcer D C Lewin and Sidney Truelove[3] (Radcliffe Infirm Oxford) note that mortality was 19 per cent both for 305 patients with hematemesis caused by various conditions and for 208 patients of the group who had chronic peptic ulcer Sex length of ulcer history previous hematemesis or severity of bleeding had no bearing on immediate prognosis Mortality increased sharply at

( ) J A M A 137 1035 1036 J ly 17 1948
(3) B t M J 1 383 386 M 5 1949

about age 50 and thereafter was about five times that in younger people

The findings suggest that general bodily changes and not local conditions in the ulcer are mainly responsible for the poor prognosis in later life Additional evidence that poor prognosis in later life is mainly due to general bodily changes is provided by the increased death rate

FATALITY RATE OF PERFORATED ULCER BY AGE GROUPS

A e G o p	P T N	D eo	Di p
Under 30	18	1	5 6
30-39	34	1	2 9
40-49	48	10	20 8
50 59	41	12	29 2
60-69	23	7	30 5
70 +	9	3	33.3
Total	173	34	19 7

associated with advancing age following perforation of peptic ulcer (see Table)

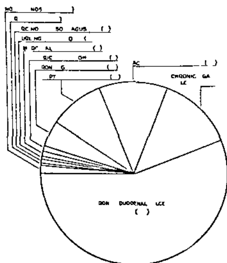
[On the other hand many would argue that the local changes characterized by depth induration scarring chronic perforation and calcification of the vessels especially extensive arrosion of a large vessel are of greater significance —Ed]

Management of Bleeding Duodenal Ulcers Robert W Fraser and John P West[4] (St Luke s Hosp New York City) reviewed records of 177 patients with severe bleed ing from duodenal ulcers in whom hemoglobin was 65 per cent or less and red cell count 3 500 000 or less Among 165 patients treated medically 7 died (4 2 per cent) among 12 operated on while actively bleeding 4 died

Among 93 under age 50 9 were operated on and 3 died while among the rest all treated medically none died Of 84 patients over age 50 3 were operated on and 1 died of 81 treated medically 7 died (8 6 per cent) Thus age is an important factor in estimating chances of sur vival Arteriosclerosis was one of the most important causes of death Pulmonary complications caused two operative deaths and failure to control bleeding was responsible for the other two

(4) Ann. S rg 129 99 304 Ja h 1949

Massive Hematemesis Analysis of 300 Consecutive Cases All patients studied by Cyril Costello[5] (Washington Univ) vomited large quantities of blood and showed evidence of shock or severe anemia or both Incidence of massive hematemesis in the 247 males and 57 females was greater between the fourth and eighth decades in both sexes and highest in the sixth decade (23 per cent



Fg 120 —C f m h mat m 300 (C rt y f C t ll C An S g 129 289 298 M h 1949)

of males) Figure 120 shows the causes of massive hematemesis in this series Over all mortality was 25 per cent the rate increasing beyond the fifth decade Bleeding from chronic gastric ulcer carcinoma of esophagus ruptured esophageal varix and marginal ulcer caused higher mortality (48 75 per cent of patients) than did bleeding due to acute or chronic gastritis or chronic duodenal ulcer (9 13 per cent)

No patient died suddenly as would be expected from

(5) A S g 129 289 98 M h 1949

persistent fulminant hemorrhage death occurred from two days to three weeks after onset of bleeding Surgical or postmortem examination disclosed that most eroded vessels were partially or completely blocked by antemortem thrombi and stomach or duodenum contained little or no fresh blood These findings and the observation that 71 of the 75 patients who died did not receive even a moderate fraction of the blood required to replace what was lost suggested that treatment should be directed toward support of depleted blood volume rather than surgical closure of the injured vessel The theory that restoring blood pressure risks the blowing out of a forming thrombus has no scientific substantiation Accordingly 73 patients whose sex and age corresponded closely to that of the previous group were treated by adequate and prompt blood replacement mortality was 4 per cent The program used follows

METHOD —A blood bank is essential since as much as 4 L. blood has been given in the first 24 hour hospital period Frequent intravenous use of saline does not re-establish blood volume and encourages pulmonary edema Plasma may be used while blood is being cross matched Blood needs are best determined by frequent repetition of the copper sulfate falling drop determination [see Kolmer J A and Boerner F Copper Sulfate Method for Determination of Specific Gravities of Whole Blood and Plasma *Approved Laboratory Technic* (New York City D Appleton Century Company Inc. 1945) —Ed] The danger of provoking hemorrhage contraindicates use of a Levin tube unless there is definite gastric distention and nausea. To maintain nutrition and support tissue repair 200 cc of the following preparation should be ingested orally every two hours 150 Gm predigested protein powder (polypeptide) 300 Gm dextri maltose * 1 Gm vitamin C 1 cc liquid multiple vitamin and water to make 2 400 cc Sedation should consist of a single dose of morphine followed by hypodermic injections of 2 gr sodium phenobarbital every two hours as needed to keep the patient drowsy Surgery should be withheld until bleeding has ceased and patients have improved so that it can be undertaken without great risk Diagnosis should be pursued only after hemorrhage has ceased and the danger of reprecipitating or exaggerating it has passed

[The preceding articles dealing with a dramatic sometimes fatal and always worrisome aspect of peptic ulcer ... thy of more

extended comment. It is generally conceded that the conventional criteria are inadequate in providing timely information as to immediate prognosis and the duration and extent of conservative measures justifiable especially with respect to transfusions following massive gastroenteric hemorrhage Hence the tendency in recent years to advocate measures other than simple laboratory ones and to apply clinical rules of thumb which can be variously interpreted Bennett Dow and Wright (194_) for example have advocated the serial determination of plasma and blood volume Other observers like the author have recommended somewhat similar procedures Such laboratory data coupled with proper evaluation of the symptoms and signs present including other factors of clinicopathologic nature make for more intelligent treatment whether medical or surgical and prognosis

The decline in mortality in the past decade especially with nonoperative measures is attributed largely to liberal transfusions of blood and early feeding which combat shock tissue anoxia oft n irreversible and eventually fatal dehydration hyperazot mia and acute malnutrition and places the patient in a much stronger position to withstand further hemorrhages The continuous drip method of transfusion introduced by Marriott and Kekwick (1935) in England is deservingly well regarded by their British colleagues Factors which have a more serious prognostic bearing in general are advanced age large size of lesion associated degenerative processes of any of the body systems and complications like acute perforation Marked elevation of the blood urea nitrogen i regarded as a serious omen Failure of improvement within 48 hours after institution of a strict regimen or occurrence of initial hemorrhage during such regimen is justification for surgical intervention without unnecessary delay according to some authorities In general bleeding from a deep indurated ga tric or gastrojejunal ulcer is usually more profuse and hence more dangerous than that from a duodenal ulcer Indiscriminate operations on bleeding patients on admission to hospital is unwise for in 16-20 per cent of such patients objective evidence of a gross gastric or duodenal lesion whether benign or malignant will not be demonstrable Palliative surgical measures such as ligation of blood vessels pyloroplasty and gastroenterostomy are usually ineffectual and risky There is a limited scope for emergency partial gastrectomy in some cases of massive hemorrhage For further details of various nature I recommend Chapter X of Volume V of *Nelson's Loose Leaf Medicine* and a much quoted contribution by F Avery Jones in the *British Medical Journal* of Sept 20 and 27 1947—Ed]

Postprandial Symptoms Following Subtotal Gastrectomy for Peptic Ulcer and Their Relationship to Glucose Tolerance Curve S E Schechter and H Necheles[6] (Michael Reese Hosp Chicago) performed intravenous and oral glucose tolerance tests on 11 patients who had had subtotal gastric resection for peptic ulcer and had early postprandial symptoms in varying degree Gastro

[6] ...oe t rology 12 258 274 F bru y 1949

intestinal manifestations of this syndrome include nausea vomiting fulness in the epigastrium belching abdominal cramps and diarrhea Generalized symptoms are weakness dizziness unpleasant sensation of warmth cold sweat headache and palpitation all of which are similar to those which may occur with hypoglycemia However they appear immediately after eating long before objective hypoglycemia develops and are due to some other mechanism thought by some investigators to be hyperglycemic shock

All intravenous tolerance curves however were normal Oral glucose tolerance curves of four patients showed no unusual hyperglycemia but three had moderate early postprandial symptoms after drinking the glucose Oral tolerance curves of four patients showed marked hyperglycemia but none had symptoms In the final group of oral tolerance curves one patient had severe symptoms but no unusual hyperglycemia one had mild symptoms and hyperglycemia and one had severe symptoms but vomited a large part of the glucose ingested *None of these findings provide evidence in* favor of the hyperglycemic shock theory

Since intravenous glucose tolerance tests were normal there is probably no fundamental disturbance in carbohydrate metabolism in these patients Early postprandial symptoms and abnormal glucose tolerance curves do not necessarily occur together and are probably not etiologically related but may be manifestations of the same abnormality the exact nature of which is not yet clear It is likely that early postprandial symptoms are due to a combination of factors such as jejunal distention jejunitis vagotonia and psychoneurosis which operate in varying degrees in different individuals

[The result of this research support the content on of several other investigators and many clinicians that disturbances of carbohydrate metabolism are not *responsible for the so-called* post ga trectomy syndrome. Despite the current conflicting opinions as to the mechanisms engendering these disturbances it is generally accepted that the rapid entrance of food into the jejunum is somehow responsible Machella recently reported the results of h s investigations on 16 patients manifesting symp the "dump

ing syndrome He observed that the symptoms occurred toward the end of a mixed meal or immediately thereafter during which time the blood sugar level is usually elevated. They were accompanied by a rise in blood pressure and an increase in pulse rate The manifestations were reproduced by the administration of glucose and sucrose orally but not when glucose was administered intravenously They were also reproduced in individuals with intact stomachs following the intrajejunal instillation of hypertonic solutions of glucose sucrose protein hydrolysate sodium sulfate and magnesium sulfate and by distention of the jejunum by an air filled balloon This investigator felt that the early symptoms of the postgastrectomy syndrome were due to distention of the jejunum by the fluid which enters the lumen of the gut in response to the presence of a hypertonic solution and not to distention by the mechanical presence of the food per se In his opinion these symptoms are not caused by hyperglycemia though hyperglycemia may be present during the period of symptoms It was found that the symptoms may be prevented by the administration of atropine in physiologic doses before meals However they are not prevented by bilateral vagotomy —Ed]

Postoperative Management of Patients with Gastrectomy MacDonald Wood[7] described the regimen used at Cincinnati General Hospital

TREATMENT —Minimal fluid intake of 3 000 3 500 cc /day is maintained unless there is a contraindication Daily parenteral administration of 1 2 L amino acids 1 L of 5 per cent glucose in water and 0 5 L of 5 per cent glucose in normal saline gives the minimal daily requirement of 100 Gm protein 150 Gm glucose and 5 7 Gm sodium chloride Five hundred mg of vitamin C 5 mg thiamine hydrochloride 5 mg riboflavin and 100 mg niacin are given routinely every day Intravenous therapy is continued four to six days or until oral feedings are sufficient Hematocrit and protein level may be maintained by whole blood transfusion if required

Close observation of the bladder during the immediate 18 24 postoperative hours is necessary to prevent overdistention Although 800 cc urine daily for the first 48 hours is not insufficient average daily output should be 1 000 1 200 cc Urinary output and fluid removed by gastric suction should be measured so that adequate replacement therapy can be calculated

Continuous Wangensteen suction through a Levin tube is maintained 36 48 hours after partial and 72 hours after total gastrectomy To maintain chloride balance 1 cc of 5 per cent glucose in saline should be given intravenously for every cubic centimeter of vomitus or aspirated material The Levin tube may be removed when audible peristalsis returns the aspi

(7) Oh St t M J 45 1 4 M b 1949

rated fluid loses its bloody character and its amount is under 200 cc /day

The third postoperative day 1 oz water is given hourly by mouth The fourth day 2 oz water on the even hour and fat free broth albumin water bland fruit juices or buttermilk are given on odd hours On the fifth day hourly feedings alternating water broth tea etc are increased to 3 oz The sixth day 4 oz hourly feedings are given and coddled egg morning and evening and eggnog at noon are added Oral feeding of amino acids in three divided doses to total 150 Gm protein is started The seventh day water is given ad lib with supplementary amino acids and surgical soft diet At eight a m are given 3 oz cereal 3 oz milk and cream and a coddled egg at noon one slice of milk toast 8 oz eggnog and 4 oz custard at 4 p m 3 oz milk and cream and a coddled egg and at 8 p m 8 oz eggnog or milk and cream or malted milk The patient should be ready for full Meulengracht diet in four divided feedings by the tenth day Those with total gastrectomy are started 24 36 hours later on the preceding diet

Early ambulation is recommended for more rapid recuperation Any postoperative rise in temperature pulse or respiration should be a signal of possible pulmonary or vascular complications Respiratory stimulation with carbon dioxide and deep breathing has decreased pulmonary complications When atelectasis is present coughing with abdominal support given by an assistant should be encouraged If this fails to dislodge obstructing bronchial mucus plugs bronchoscopy should be carried out and repeated in the event of recurrence Persistent tracheobronchial mucus secretions can be treated by insertion of a small catheter through the nose into the trachea Anticoagulants should be administered at the earliest signs of thrombophlebitis

Ingestion of a small amount of barium shows whether gastric retention is due to obstruction at the stoma or in the upper small bowel Reoperation to correct a persistent malfunctioning stoma is to be condemned but jejunostomy is indicated in all cases

In patients in whom duodenal fistula develops fluid balance must be maintained and the skin protected from erosion Jejunostomy is imperative for feeding and returning aspirated secretions from the fistula Putting the patient on his abdomen on a Bradford frame keeps digestive juices from accumulating on the skin Fuller s earth aluminum paste or peptones may be applied around the fistulous opening Fistulas usually close but after persisting for months may require operation with implantation of the tract into bowel

Radiation Therapy in Peptic Ulcer Analysis of Results William E Ricketts Walter Lincoln Palmer Joseph B Kirsner and Anna Hamann[8] (Univ of Chicago) analyze results of x ray therapy of the fundus and corpus of the stomach in over 800 cases of peptic ulcer studied from 1936 to 1947 Treatment is based on the facts that acid gastric juice is essential for development of chronic peptic ulcer and that irradiation depresses the secretory capacity of the stomach Three to eight treatments through 2 portals were given over 6-14 days to a total dose of 600 2 500 r

There was a direct correlation between decrease of hydrochloric acid and total amount of radiation delivered but no correlation between duration of ulcer (gastric duodenal or jejunal) or age of the patient and healing of ulcer With abolishment of free hydrochloric acid a direct correlation was apparent A higher incidence of postradiation achlorhydria occurred in patients with gastric ulcer than in those with duodenal or jejunal ulcer Ulcer pain disappeared during achlorhydria No symptoms attended radiation achlorhydria

In 47 patients with gastric ulcer hydrochloric acid depression occurred promptly in two thirds within less than a month Coincident were inflammatory changes in the mucosa evident gastroscopically and histologically Duration of the achlorhydria was variable the shortest period being a few days and the longest eight years Healing occurred in 90 per cent of 50 cases In 114 patients with gastric ulcer treated by medical management alone there was a 60 per cent incidence of healing Recurrence was observed in a third of the patients followed 1 10 years and in 80 per cent of the patients treated medically There was no correlation between age of patient and recurrence All recurrences appeared within two years after radiation Only 20 per cent of patients who had achlorhydria of three months or longer had recurrences

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out symptoms and secretory response to hypoglycemia Failure to sever all vagus fibers is therefore not an adequate explanation of re establishment of hypoglycemic reflexes There must be hypothecated either anatomic regeneration or some physiologic reassumption of cholinergic function

Vagus resection is not a cure for duodenal ulcer but is a physiologic procedure which by removing most parasympathetic nerves to the upper gastrointestinal tract makes management of patients with duodenal ulcer simple rather than complicated Variations in procedure which may produce protection against ulcer without incurring side effects should be further studied Re investigation of the anatomy of the vagus nerves below the diaphragm revealed that most fibers of the right vagus nerve appear to go directly to the celiac ganglion or to other gangliionated masses of nerve tissue in the aortic region From this area fibers are given off anteriorly which pass to the stomach It is therefore possible to divest the stomach of the fibers from the right vagus without at the same time severing the right vagus fibers to the celiac ganglion In one patient in whom right vagus fibers to the celiac ganglion were left intact but left vagus fibers severed in toto clinical by products of vagotomy were not lessened

[Five or more years following the institution of med cal treatment or operation for ulcer one is in a better position to evaluate such procedure properly The t me is fast approaching when vagotomy can be evaluated regarding both its effect on the lesion and the well known side effects Personally of course I would never permit anyone to sever my silver co ds of life" except perhaps under the most extenuating circumstances It seems significant that two distinguished American surgeons of large experience have independently arrived at almost identical conclusions regarding the virtues and shortcomings of bilateral vagotomy Briefly stated in their judgment vagotomy as a sole procedure should be abandoned it is not indicated in the treatment of gastric ulcer the approach *should be via the infradiaphragmatic route so that* the clinical diagnosis may be confirmed and the true nature of the lesion if present be ascertained Such procedure al o admits of general abdominal exploration However these authorities feel that ga troenterostomy combined with vagotomy is the operation of choice in cases of duodenal ulcer unsuitable for subtotal gas trectomy the latter procedure remains the method of choice in

Of 362 patients with duodenal ulcer 108 had achlorhydria which lasted less than three months in two thirds but was usually unpredictable in one patient lasting eight years Of 156 patients followed 1 10 years two thirds of those receiving minimal radiation and about one third of those receiving larger amounts had a recurrence It developed within six months to two years after healing in some cases immediately after reappearance of acid in the gastric secretion In others recurrence did not take place despite reappearance of acid Again achlorhydria for longer than three months was associated with a higher incidence of healing

In 19 of 20 patients with jejunal ulcer healing occurred In the unhealed case gastric secretion was not depressed The ulcer recurred in 9 of 17 patients followed longer than one year

The authors conclude that radiation of acid secreting portions of the stomach is valuable in treatment of peptic ulcer The effect is proportional to the reduction of gastric secretion

Follow Up of Vagotomy in Duodenal Ulcer is reported by Francis D Moore[9] (Massachusetts Gen l Hosp) Of 116 patients operated on by vagus resection and studied for 5-45 months 13 had recurrence Eight had frank recurrence of ulcer symptoms with x ray changes or x ray changes alone Five had recurrence of symptoms without demonstrable x ray pathology At the time of this report all but 2 of the 13 patients were well without further therapy other than simple dietary precautions Essential features in the cases of recurrent ulcer were a history of complete relief and healing after vagotomy followed after a long interval by disappearance of side effects of vagotomy and reappearance of ulceration with mild or insignificant symptoms and restoration of a delayed secretory response to insulin

Re establishment of gastric secretory response to insulin induced hypoglycemia has been observed two to four years after vagotomy despite a long interval with

(9) Gastroenterology 11 442 452 October 1948

epigastric hernia On the other hand those with epigastric hernia and ulcer syndrome or vague visceral complaints must have adequate x ray examinations before undergoing surgery for the hernia Trial medical management may relieve symptoms in five of the authors patients this procedure made surgery unnecessary If operation is done the abdomen should be explored at the time of repair regardless of negative preoperative diagnostic study In six such patients exploration revealed specific lesions a stellate scar of duodenum chronic cholecystitis gallbladder adherent to mesocolon duodenal ulcer perforated against gallbladder and two acute duodenal ulcers In two patients hernia repair was completed without recognition of acute duodenal ulcer or periesophageal hernia Four patients in whom hernias were repaired returned later because of severe and persistent upper abdominal pain one had atrophic gastritis one year after surgery another had gastric hemorrhage two years later one had eventration of the left side of the diaphragm with narrowed pyloric antrum four years later and the other bled from penetrating gastric ulcer eight years after hernia repair Gastric hemorrhage two years after diagnosis caused the death of one patient who had not undergone surgery

[In the presence of a hernia of this nature esophageal hiatal hernia or gastric or duodenal diverticulum it is always the better part of wisdom first to exclude other pathologic processes as the cause of the symptoms presented Of course such hernias or diverticula may on occasion be the sole disturbing factor —Ed.]

Diverticula of Stomach To the 150 cases of true diverticulum of the stomach reported in the medical literature S P Bralow and M A Spellberg[2] (Chicago) add 26 cases At Veterans Administration Hospital Hines Ill where most of these cases were observed the estimated incidence of this condition was 0 015 per cent of total admissions during the past 12 years Ages of the patients ranged from 20 to 67 years Mechanism of development of gastric diverticula is not entirely agreed on but it is the consensus that diverticula should be

G st oe t l gy 11 59 82 J ly 1948.

duodenal ulcer vagotomy effects excellent immediate results in the treatment of anastomotic ulcer following either gastroenterostomy or subtotal (partial) gastrectomy In patients considered to be good postoperative risks a subtotal gastrectomy with or without infradiaphragmatic vagotomy is *preferable to vagotomy* alone for gastrojejunal ulcer following gastroenterostomy for such ulcer following subtotal gastrectomy resection of the ulcer and further gastric resection if possible combined with vagotomy is preferable to vagotomy alone Completeness of the division of vagi as evidenced by insulin test bears no relation to clinical results whether the incidence of gastrojejunal (anastomotic) ulcer will be lessened by a combination of vagotomy and gastroenterostomy as compared to gastroenterostomy alone remains to be seen

According to Thomas extensive experience with vagotomy has revealed that impairment of gastric motor and secretory function is more persistent in man than in experimental animals following comparable operations The evidence suggests that complete vagotomy if it were possible might be dangerous —Ed]

***Coexistence of Intra abdominal Lesions in Patients* with Epigastric Hernia** John M Hoffman and Gregg D Wood[1] (Portland Ore) emphasize that in patients with epigastric hernia pain in the upper abdomen may be caused by a coexistent visceral lesion rather than by the hernia Among 76 patients with epigastric hernia admitted to the Portland Veterans Hospital were 24 who came because of upper abdominal pain which the examining physician attributed to hernia but which subsequent observation or operation showed was due to such lesions as acute duodenal ulcer or acute cholecystitis

Symptoms of epigastric hernia are sharp finger point lancinating pain on straining well localized to the hernial ring where filaments of lower intercostal nerves are impinged and deep boring aching pain aggravated by eating or bending backward produced by drag on the greater omentum greater curvature of the stomach or falciform ligament of the liver Pain is relieved *on reduc*tion of mass or lying down These symptoms were observed in 30 patients

Patients with vague x ray changes and poor response *to* therapy for suspected biliary or upper *gastrointestinal* disease should have careful detailed examination for

(1) Surgery 25 566 574 April 1949

associated pathologic processes which might have produced them Symptoms included epigastric pain vomiting bloating weight loss melena hematemesis pyrosis weakness and dysphagia Pain vomiting and hemorrhage were sometimes incapacitating

Radiologic diagnosis depends on retention of opaque medium which is usually seen after the stomach empties Gastroscopy may visualize the opening of the diverticulum The pre and postoperative x ray appearance in one case is shown in Figures 121 and 122 the artist s impression of the gastroscopic picture of the opening of the diverticulum about one year after operation is shown in Figure 123

Medical therapy includes use of bland diets lavage postural drainage and antispasmodics The authors recommend total extirpation of gastric diverticula rather than the simple purse string suture used in the case illustrated

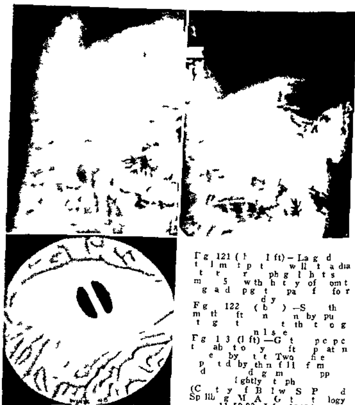
Experience with Screening Tests in Detection of Cancer is reviewed by David State[3] (Univ of Minnesota) A study was started in 1945 to determine the presence of gastric cancer in persons without symptoms All persons over 50 who registered at the outpatient department of University Hospital had gastric analysis after histamine stimulation Gastrointestinal x ray series were made on all with achlorhydria and hypochlorhydria to broaden the scope of the study x rays were also taken of various other groups (Table 1) Patients tested by Wetherby in 1940 for histamine achlorhydria were recalled and restudied Results in the entire series were compared with those reported by two other groups of investigators (Table 2)

The most important finding in the present study was 29 gastric polyps One purpose of this study was to ascertain whether or not gastric polyps become malignant Three polyps have shown evidence of conversion to malignancy

Results of this study led to establishment of a cancer

(3) M ta M d 32 57 61 J y 1949

classified as either true congenital or false acquired True diverticula are protrusions of the mucosa and sub mucosa through congenitally weak muscular layers Ac quired diverticula are more frequent near the pylorus



Fg 121 (l l ft) – La g d t l m t p t w ll t a dia t r r ph g l h t s m 5 w th h t y of om t g a d p g t pa f fo r d y

Fg 122 (b) —S th m tt ft n n by pu t g t t th t o g n l s e

Fg 1 3 (l ft) —G t p c p c t ab t o y ft p at n e by t t Two fi e p t d by th n f 1 1 f m d d g m pp l ghtly t ph

(C t y f B l w S P d Sp llb g M A G t t logy 11 59 82 J ly 1948)

and are thought to be due to traction from contiguous infections or neoplasms

Symptoms and signs of diverticulum of the stomach are not characteristic and diagnosis cannot be made without roentgenograms or gastroscopy All of the au thors patients had gastrointestinal sym ᵗ ıt 15 had

of large bowel malignancy or vague symptoms that could be attributed to malignancy of the large bowel Among 281 persons examined during the first two months 2 had cancer of the rectum 1 cancer of the cecum 38 rectal polyps and 1 gastric polyposis

Significance of Ulcerating Lesion in Stomach after Gastroenterostomy Howard K Gray and Karl A Lofgren[4] state that every lesion occurring in the stomach after gastroenterostomy should be treated as malignant until proved otherwise because a high proportion of ulcerating gastric lesions which develop after such an operation are malignant It has been generally accepted that coexistence of an active duodenal ulcer and gastric carcinoma is rare Eusterman and Balfour reported that of 15 985 patients examined roentgenographically because of digestive disturbance 2 047 (12 8 per cent) had deformities of the duodenal cap characteristic of duodenal ulcer 167 (1 per cent) had evidence of gastric ulcer only 24 (0 15 per cent) had evidence of both duodenal and gastric ulcer and none had evidence of duodenal ulcer associated with an apparently malignant gastric lesion Fischer Clagett and McDonald found 48 cases of coexistent duodenal ulcer and gastric carcinoma in the surgical and autopsy files of Mayo Clinic for 1911 44 but in only 1 case had gastroenterostomy been performed previously for duodenal ulcer

Data on 825 consecutive patients seen between Jan 1 1938 and Dec 31 1947 were reviewed All had had gastroenterostomy previously for duodenal or gastric ulcer Because of subsequent complications the stoma was taken down and partial gastrectomy performed Forty one gastric lesions had developed after gastroenterostomy for duodenal ulcer and of these 11 (27 per cent) were carcinomas Of 11 gastric lesions that developed or were retained after gastroenterostomy for gastric ulcer 6 (55 per cent) were malignant Interval between operations was two years or less in five of six patients One may assume that the original lesion may not have been

(4) Proc Staff Meet Mayo Clin 23 454 460 Sept 29 1948

detection center Patients are examined as a whole without concentration on any particular organ of the body In addition to several routine laboratory tests gastrointestinal series are made on patients with histamine achlorhydria or hypochlorhydria (less than 30 degrees

TABLE 1 —X Ray Results from July 1 1945 to May 1 1948

	Patients	GI Series	Polyps	Cancers
Achlorhydria	911	1 168	19 (+13 ques)	7*
Hypochlorhydria	90	52	—	—
Wetherby list	110	113	6 (+1 ques)	—
Pernicious anemia	70 (26 new) (44 old)	136	4†	2
Relatives of persons with gastric cancer	67	67	—	—
Patients with hemoglobin level of 11 Gm or less	45	45	—	—
Patients with occult blood in feces	87	75	—	—
	1,380	1 656	29	9

* Tw add t o l ca c m d th gh g n z t at e r and on m ssed by x ray a d u co r d at p ation f n el ted c nd tion
† O e polyp f u d po t m tem two addit l polyp found at gastr s py and m sed by x ray

TABLE 2—Comparison of Results with Those of Other Investigators

Investigators	Patients Receiving GI Studies	Finding
St John Swenson and Harvey (1944)	2 413 over 50 without gastric complaints	2 carcinomas 1 lymphosarcoma
Daily and Miller (1945)	500 men over 45 presumably free from digestive complaints	1 benign gastric ulcer 1 polyp 1 antral gastritis
Univ of Minnesota (1945 48)	1 111 over 50 free from digestive complaints with histamine achlorhydria and hypochlorhydria	7 gastric cancers 25 gastric polyps

free acid) occult blood in the stool family history of gastric carcinoma unexplained hemoglobin level below 11 Gm or vague symptoms of gastric pathology Barium enemas are given patients with abnormal findings on proctoscopic examination occult blood in the stool unexplained hemoglobin level below 11 Gm amily history

of large bowel malignancy or vague symptoms that could be attributed to malignancy of the large bowel Among 281 persons examined during the first two months 2 had cancer of the rectum 1 cancer of the cecum 38 rectal polyps and 1 gastric polyposis

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(4) P oc Staff M t M o Cl 23 454 460 S pt 29 1948

a benign gastric ulcer Biopsy or local excision of gastric ulcer at gastroenterostomy would be helpful and might change the original surgical attack to a more radical one at an earlier and more favorable time In one patient gastroenterostomy was performed for another reason and a gastric carcinoma developed subsequently

The true nature of a lesion in a stomach in which gastroenterostomy has been performed is often difficult to determine clinically Symptoms and clinical data may give the impression of a benign lesion when the underlying condition is malignant X ray examination is more difficult because of the frequent marked structural changes obstructive features and inflammation

Duodenal Spread of Pyloric Carcinoma J H Fodden[5] (Univ of Liverpool) studied 21 autopsy and 29 surgical

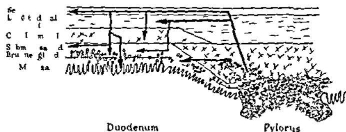


Fig 124 —Main pathways of cancer spread from pylorus into tissues of duodenum (Courtesy of Fodden J H Brit J Cancer 2 239 249 September 1948)

specimens of pyloric cancer and found duodenal spread of tumor in 7 of the former and 9 of the latter In five surgical specimens cancer cells had reached the edge of the resection

Infiltration took place more frequently along the duodenal continuation of the lesser curvature than along that of the greater curvature Most sections showed that lymphatic cancer spread in pyloric submucosa was partially but not completely checked at the sphincter Other sections showed cancer from gastric submucosa traversing

(5) Brit J Cancer 2 239 49 Sept 1948

lymphatic channels through the circular sphincte cle of the pylorus to reach outer muscular and sub layers Several routes of spread were seen (Fig 1 occurred mainly through lymphatics of the du wall but in some instances tumor invaded duode sues directly Duodenal mucous membrane and the ner gland layer were the only tissues which re i vasion by cancer

In all but one surgical case duodenal extension cer was microscopic There was no single macr feature which indicated whether or not infiltrati taken place

Gastric Cancer Morphologic Factors in Fiv Survival after Gastrectomy Paul E Steiner San Maimon Walter L Palmer and Joseph B K (Univ of Chicago) compared gross and microsco servations on 30 patients with gastric cancer livi or more years after resection with similar obser on 30 patients who died of local recurrence or met within one year postoperatively They found three scopic features of prognostic significance for lo vival In the five year survivors 25 tumors gre circumscribed manner There was a distinct dema without root extension between tumor and host peared as though the tumor advanced through tl tric wall *en bloc* In the short term survivors a degree of circumscription was found only twice

A second important factor in prognosis is th histologic types of cancer (represented in nine were found only in the five year survivors In si the tumors were composed of groups and solid c medium sized polyhedral cells with large pale nuc little cytoplasm The stroma was rich in inflam cells Under low power magnifications hematoxy eosin sections appeared distinctly bluish causi tumors to be referred to as blue cell cancers The genetic nature of these tumors could not be ide The second cell type associated with a good pr

was the well known undifferentiated small cell carcinoma (or sarcoma)

In 14 long term survivors retrogressive change of the tumor cells was regarded as of prognostic significance It consisted of atrophy and distortion of tumor cells and pyknosis of their nuclei and was most conspicuous at the advancing border The common types of degenerative change such as massive necrosis were less frequent in the five year survival group than in controls

Macroscopic typing is of little prognostic significance because finer degrees of tumor circumscription cannot be detected Since histologic grading does not take into consideration the favorable course of a few special types of undifferentiated cancer or the importance of circumscription or retrogressive changes it is not wholly satisfactory for estimating prognosis

[Although the series may be too small to permit of definitive conclusions this study suggests factors gross and microscopic, apart from glandular involvement other than those we consider to be of prognostic significance —Ed]

Carcinoma of Stomach Validity of Basing Prognosis on Borrmann Typing or Presence of Metastases Analysis of data on 124 patients whose stomachs were resected for gastric carcinoma led George E Moore David State Robert Hebbel and Alan E Treloar[7] (Univ of Minnesota) to conclude that presence or absence of demonstrable metastases in regional nodes has a greater prognostic value than Borrmann typing of the tumor Borrmann separated gastric carcinomas into four gross types I sharply demarcated polypoid II sharply demarcated ulcerated III partly infiltrating and IV diffusely infiltrating Combining types I and II as limited and types III and IV as infiltrative groups Schindler noted that the former group is characterized by a much higher resectability rate and lower mortality rate

In the present series 17 of 67 patients with infiltrating tumors survived at least three years and 8 of the 17 showed no metastases Of 33 patients with limited tumors 21 failed to live three years and of these 18 had

(7) S rg Gyn c. & Ob t. 87 513 518

metastases About 70 per cent of the patients without metastases survived three years In the presence of lymph node involvement the possibility of survival decreases to about one fourth this figure It therefore seems that attempts to predict survival of patients with carcinoma of the stomach by gastroscopic typing of the lesion are not justified

Borrmann typing influences prognosis to the extent that limited tumors provide a proportionately larger number of cases free from metastases whereas the more numerous infiltrating tumors are more likely to have metastasized Presence or absence of metastases cannot be determined accurately before operation No patient should be denied operation because of the type of tumor he may be determined to have

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HEPATOBILIARY AND PANCREATIC SYSTEMS

Further Observations on Production and Prevention of Dietary Hepatic Injury in Rats The studies of Paul Gyorgy (Univ of Pennsylvania) and Harry Goldblatt[8] (Cedars of Lebanon Hosp Los Angeles) were carried out during the last nine years on 1 922 rats Massive or zonal hepatic necrosis may be caused by deficiency of several dietary factors singly or in combination among which are sulfur containing amino acids (cystine and methionine) and vitamin E In the development of acute diffuse hepatic necrosis tocopherol may compensate for absence of cystine and/or methionine and vice versa Cod liver oil and lard with their high content of unsaturated fatty acids enhance the development of acute massive and zonal necrosis probably by promoting tocopheral destruction while butter and Crisco which are low in unsaturated fatty acid content retard or prevent necrosis

The interchangeability of sulfur containing amino

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acids and vitamin E makes it difficult to accept pure deficiency as the basis of acute hepatic necrosis Possibly endogenous hepatotoxic substances are neutralized by cystine or tocopherol Although these factors are important in the etiology of hepatic necrosis there are probably others yet to be defined In addition it is difficult to distinguish between mechanisms based primarily on deficiency or intoxication

Diffuse hepatic fibrosis occurred regularly in rats on a diet low in lipotropic factors Choline methionine methionine containing protein such as casein and vegetable shortening will prevent or reduce while cystine lard and cod liver oil will enhance the production of hepatic cirrhosis There is no visible link between specific cirrhosis producing effect of certain fats and lipotropic or antilipotropic factors Diffuse fibrosis is unaltered by tocopherol in rats receiving lard and cod liver oil Ceroid deposit accompanies cirrhosis only in rats which have been kept on a cirrhosis producing diet of fats with a high content of unsaturated fatty acids (cod liver oil lard) and tocopherol will not prevent ceroid formation

Careful study of the histologic picture disclosed that fibrotic changes begin not in portal spaces but close to central veins with a distribution of connective tissue around these veins which is different from that of so called central cardiac cirrhosis Bands of connective tissue later radiate from the region of these veins to join fibrous tissue around other central veins and even portal connective tissue Necrotic cells are found commonly singly or in small groups in and around the fibrous bands of cirrhotic livers but it cannot be determined whether cellular injury follows precedes or accompanies fibrotic changes Fat infiltration and cirrhosis are not related since the former may be present with or without cirrhosis

Renal changes in the form of necrotizing nephrosis (acute healing or healed) were often seen accompany

ing acute hepatic fibrosis but their courses on the same diet were not necessarily identical

[The current observations and conclusions reached by two pioneer investigators in the important field of experimental dietary hepatic injury should be of interest to the reader The bibliography cites the significant contributions to the subject by other workers A guarded and conservative attitude and a commendable one under the circumstances is characterized by the following statements It is questionable whether with all these dietary factors the etiology of massive hepatic cirrhosis is completely defined The int r changeability of sulfur containing amino acids (cystine methionine) and vitamin E as leading etiologi factors makes it difficult to accept pure deficiency as the basis of massive hepatic cirrhosi —Ed]

Anicteric Hepatitis Report of Nine Sporadic Cases During the winter of 1946-47 Hyman J Zimmerman and Lawrence J Thomas[9] (George Washington Univ) observed nine cases which appeared to satisfy the criteria of anicteric hepatitis marked upper abdominal complaints and laboratory evidence of liver damage after a nonspecific febrile illness Clinical features were those of a systemic disease with predominant abdominal localization (see Table)

Lymph nodes were enlarged in seven cases Tenderness in the epigastrium or right upper quadrant was present Other abnormal physical changes were rare In all cases white blood cell count was within normal limits or slightly depressed In three an eosinophil count of 5 per cent was noted initially Urine urobilinogen was elevated in all Results of bromsulfalein retention cephalin flocculation and thymol turbidity tests indicated impaired liver function

Abdominal involvement became more evident with subsidence of fever Epigastric fulness anorexia flatulence and epigastric or right upper quadrant abdominal tenderness were prominent The course varied from 3 to 20 weeks One patient showed excessive fatigability anorexia abdominal fulness and weight loss as well as impaired liver function at the end of 20 weeks

The cause of anicteric hepatitis is not known Recogni

(9) Am J M S 216 545 550 N mb 1948

Clinical Features

Occupa io	Age	Symptoms										Signs			
		Ch lly S sat	F	M l	Fat gu	Ep g t F l	A e a	\	V m t g	H da he	S e Th at	Ade p thy	H p tom galy	Ep g st c Tende n ss	R U Q T de ness
Physician	27	0	0	/	/	/	/	X	0	0	0	/	/	/	/
Nurse	21	/	/	X	/	/	/	/	0	X	/	/	/	/	/
Hou ewife	23	X	X	/	/	/	/	/	X	/	0	/	/	/	/
Physician	29	X	/	X	/	/	/	0	0	/	/	/	/	0	X
Housewife	25	X	/	X	/	X	X	0	0	X	0	/	X	/	X
Housewife	24	X	/	X	/	X	/	/	0	/	/	/	/	X	/
aborer	22	/	/	/	/	X	/	0	0	X	0	/	/	/	0
ocial wk	29	0	/	/	X	/	X	0	0	0	0	0	/	/	X
borer	24	/	/	/	X	/	/	X	0	/	0	0	/	/	/

tion of sporadic cases is important so that proper treatment may be instituted and chronic hepatitis averted Maintenance of a high caloric high protein diet and bed rest is recommended

Results of Liver Insufficiency Hansjurgen Oettel[1] (Berlin) includes among the clinical symptoms of liver insufficiency pruritus hemorrhagic diathesis bradycardia vomiting restlessness fever difficulty in breathing and cerebral symptoms Hepatic damage leads to accumulation of toxic materials ordinarily taken care of by the liver among these are oxyacids phenoxylactic acid phenol cresol indole scatol indolacetic acid and cyanides Some of these are responsible for the bad smelling breath in liver disease Destruction of liver tissue itself liberates toxic materials from decomposition of protein products peptones and toxic amino acids One of the early and characteristic signs in hepatic coma is increase in aromatic substances protein decomposition products and cyanides in the blood at times when results of the usual blood chemistry tests are within normal limits The peptones and similar protein derivatives may be responsible for fever and collapse

A decrease in bile acid content of the blood and tissues is common changes in blood constituents seen with biliary obstruction are not found in hepatic dysfunction itself Loss of bile acids leads to poor vitamin K absorption and as a consequence diminution in prothrombin formation With hepatic malfunction there is diminution in fibrinogen formation These factors contribute greatly to the hemorrhagic diathesis in liver disease However even when fibrinogen and prothrombin values are normal there may be hemorrhagic diathesis early in liver damage This is attributed to a decrease in capillary resistance the exact cause of which is unknown Changes in tissue permeability with accumulation of salt in the tissues may be a contributing factor Certainly this condition is partly responsible for the pulmonary edema so often found and for cerebral edema and edema of the

[1] [illegible] S hw m d W h s h 78 833 835 1948

respiratory center The last form of edema is responsible with some direct effect of toxins accumulating in liver damage for diminution in respiratory volume and occasional apnea often found in liver insufficiency

Secondary changes result from the kidney malfunction which follows liver damage there are oliguria and albuminuria with changes in urea uric acid and ammonia levels attributed to malfunction of the liver

Appearance of cholemia after occlusion of the biliary tree produces numerous symptoms many of which are due to liver damage which is a frequent concomitant of the biliary occlusion and not to accumulation of bile acids and salts

Xanthomatous Biliary Cirrhosis Clinical Syndrome H Edward MacMahon and S J Thannhauser[2] (Tufts College) present detailed clinical histories of five patients observed over a long period with laboratory data descriptions of four biopsy specimens taken early in the disease and three autopsy reports Xanthomatous biliary cirrhosis (pericholangiolitic biliary cirrhosis) is characterized clinically by plain and tuberous skin xanthomas enlarged liver and spleen obstructive jaundice of years duration total serum cholesterol and lecithin values four to eight times normal and low values for neutral fat in serum Serum is transparent not creamy Typical lipid values in a case reported by Eusterman and Montgomery in which liver biopsy was reviewed by MacMahon are given in the table

With two exceptions all cases reported in the literature have been in women aged 30 50 In none was a familial occurrence noted

Biopsy specimens taken early when cholesterol and lecithin values are extremely high show a nonspecific proliferative and exudative inflammatory reaction most concentrated about the junction ducts (canals of Hering) and terminal bile ducts at the periphery of the liver lobules The inflammatory tissue blocks canaliculi destroys liver cells and collapses many sinuses The large

(2) A n Int M d 30 121 179 J y 1949

bile ducts are patent and emptv and there is bile stasis No foam cells are seen in the liver tissue

At autopsy there is cobbling of the liver with striking enlargement and advanced cirrhosis Microscopically the initial and characteristic pericholangiolitic changes are difficult to see There are extensive fibrosis with fragmentation of some lobules and total loss of others degeneration of liver tissue patchy bile stasis intralobular lipoid deposition and active chronic inflammatory reaction in portions of the interstitial tissue Such a picture

VALUES FOR PLASMA LIPIDS*

	3/ 4/41	5/17/41	5/ 6/41	7/8/41	7/ 5/41	9/1 /41	1 /11/41	4/15/4
Total cholesterol	1,3?0	1,388	1 388	1 193	926	8?0	1 155	352
Cholesterol present as esters		666	980	374	443	6 5		
Lecithin		? 592	1 668	1 087	1 800	1 330	1 000	5 5
Total fatty acids		2 107	1 669	808	2,240	800	6?0	
Neutral fat†		Neg	Neg	Neg	Neg	Neg		

I m ll g m p h d d cub t m t F m E t m n d Montg m ry G t oe t l gy 3 275 286 O tobe 1944
†V l f t l f t w t h rted by E t m n d Mo tg m but w l l t d d g to th f m l f Th h se d R t by bt t g th m f f tty d p t h l t l st d gly l t p se t th l th f m th figu tab l t d f tot l f tty d

in absence of any obstruction in the large bile ducts justifies recognition of a special type of cirrhosis which may be designated anatomically as pericholangiolitic biliary cirrhosis

Increased new formation of cholesterol and lecithin by the liver and impaired excretion resulting from obliteration of the finest bile and junction ducts may be responsible for the clinical features of the syndrome Various laboratory and clinical observations favor such an explanation

[Those interested in xanthomatous diseases and the lipidoses are familiar with the publ cation of Thannhauser and his various associat s This contribution to our knowledge of a rare and in

variably fatal disease entity is very complete from both a clinical and a pathologic standpoint The authors conclusions with respect to etiology and pathogenesis seem consistent in the light of present knowledge —Ed]

Hepatic Coma Clinical and Laboratory Observations on 40 Patients T Lynch Murphy Thomas C Chalmers Richard D Eckhardt and Charles S Davidson[3] (Harvard Univ) state that liver coma is a distinct clinical syndrome characterized by progression from lethargy to noisy confusion to coma and usually to death Cases usually fall into two groups uncomplicated hepatic coma in which no cause for death other than liver disease is found and complicated hepatic coma in which severe liver disease is associated with some major complication such as infection hemorrhage or intolerance to sedation which plays an important part in precipitating the coma

Experience with 20 cases in each group indicated that aside from evidence of severe liver disease physical examination and laboratory findings during coma are not distinctive nor significantly different from precoma findings Six patients with complicated coma had bacteremia Laboratory tests were of no help in elucidating the pathogenesis of the coma In the uncomplicated group 14 patients died within the first 2 days and only 5 were living after 20 days All patients in the complicated group died

Treatment is generally unsatisfactory An adequate intake of nutrients during coma either by stomach tube or parenterally or both is essential Vitamins C K and the B complex were usually added to 1 3 L of 5 20 per cent dextrose solution administered daily by the parenteral route Thiamine supplements subcutaneously unrefined liver extract protein hydrolysate solution and central nervous system stimulants and analeptics were given to many of the patients It was found that analeptics including concentrated dextrose solution sodium succinate caffeine and benzedrine sulfate* had no effect on the comatose state In the uncomplicated group chemother

(3) N w E gla d J Med 239 605 61 Oct. 21 1 _

apy was used to prevent infection especially broncho pneumonia In the complicated group vigorous treatment of the complicating factor was undertaken

[This is an instructive contribution to our knowledge or lack of it of that most dreaded and almost invariably fatal terminal aspect of acute hepatic necrosis and chronic hepatic fibrosis (cirrhosis) The clinical manifestations are almost exclusively confined to progressive disturbances of the psyche in the authors opinion In this connection Eppinger (1940 YEAR BOOK OF GENERAL MEDICINE, p 825) characterizes the symptoms and signs of acute yellow atrophy as fast pulse nonreacting wide pupils significant odor of expired air ecchymoses comatose state and absence of splenic enlargement We are informed that the usual laboratory tests neither warn us of impending coma nor help us in elucidating its pathogenesis That biochemical abnormalities apparently exist in patients with hepatic disease which may play an important role in the genesis of coma is suggested by an investigation of Snell and Butt who observed increased amounts of lactic and pyruvic acid in the blood of patients in hepatic coma and who noticed a favorable clinical response to the administration of parenteral glucose niacin and thiamine —Ed]

Effect of Antitoxic Principle on Hepatobiliary Diseases Juan Nasio[4] (Rosario Argentina) administered a new liver extract to 450 patients with liver disease This extract was first prepared in 1926 in Japan and has since been made by workers in the United States and in South America It is distinct from that ordinarily used in treatment of pernicious anemia Its antitoxic properties have been emphasized

A number of experiments were carried out with this substance (necroton®) on small groups of patients to determine its influence on various liver functions and other physiologic functions Administration caused an increase in sedimentation rate red and white blood cells and hemoglobin did not influence blood calcium concentration or prothrombin time lowered serum nonprotein nitrogen concentration shortened bleeding and coagulation times lowered serum cholesterol concentration in most instances lowered blood sugar and stimulated gastric secretion of hydrochloric acid

The effect of this extract is evaluated most accurately by repeated hippuric acid tests during its administration

Average dose should be 3 cc daily The extract is in

⁴ t l gy 15 877 910 D mb 1948

jected intramuscularly in most patients but in advanced cirrhosis intraperitoneal injection is recommended Favorable effects attributed to this substance include diminution of toxicity disappearance of jaundice itching and hemorrhagic manifestations return of normal color in stools and urine increased excretion of bile into intestinal tract and stimulation of diuresis

The most favorable results were achieved in patients with toxic jaundice Jaundice from metals or drugs responded well In obstructive jaundice results were less striking In cirrhosis there was obvious but not always marked improvement No unfavorable reactions were noted

[The all important role of the liver s detoxicating function is generally conceded. If liver extracts with potent antitoxic properties have been developed it is reasonable to assume we have arrived at another milestone in our progress toward fuller understanding of hepatic physiology and more effective therapeutic methods I have already called attention to Sato s yakriton (1939 YEAR BOOK OF GENERAL MEDICINE p 740) As all his clinical and experimental investigations and those of other Japanese workers were reported exclusively in a Japanese medical journal in Formosa our knowledge of these researches was obtained tardily from summaries appearing in *Chemical Abstracts* and *Presse médicale* (1936) North American investigations along similar lines are limited to those of Forbes and his associates (Forbes antinecrotic principle) The crystallized principle necroton* developed by Villela of Brazil and several of his countrymen by following in general the technic of Forbes and Neale is said to have a more general antitoxic effect and causes no unfavorable reactions Claims as to its therapeutic efficacy await confirmation by other clinical investigators —Ed]

Variations in Serum Proteins in Liver Diseases with Special Reference to Their Diagnostic Significance were studied by Harald A Salvesen and Olav Lodoen[5] (Oslo) To establish normal values serum protein values were determined in 20 normal subjects Serum albumin concentrations ranged between 3 9 and 4 97 per cent globulin between 1 69 and 2 93 per cent and albumin/globulin ratio between 1 49 and 2 85 Serum protein values were then determined in 148 patients with liver diseases

Among 24 patients with acute benign hepatitis the highest albumin/globulin ratio was 1 71 and the lowest

(5) Acta m d S a d n 130 5 5 558 39

0 57 Among 25 patients with hepatitis which became chronic or ended fatally the ratios were always below 1 except in two patients with temporary improvement In toxic hepatitis from medication ratios were normal in three and below 1 in two patients

Ratios were below 1 in every one of the 26 patients with cirrhosis on whom determinations were made In a case of thrombophlebitic splenomegaly the ratio fell below 1 as cirrhosis developed Among 11 patients with gallstone occlusion and icterus ratios were above 1 except when cholangitic cirrhosis developed Ratios were normal in nine non icteric patients with gallstones In 7 patients with obstructive jaundice due to cancer ratios were lowered but were never below 0 9 except in far advanced cancer with ascites and edema In 10 patients with cancer hepatitis but without jaundice ratios were above 1 in all but one patient who was cachectic and had anasarca Ratios were slightly reduced but above 1 in six of seven patients with carcinomatosis or sarcomatosis Of six patients with liver enlargement due to various causes ratios were above 1 in five Ratios were very high in all but one of seven patients with hemolytic jaundice The value for this patient was 1 16

The Takata reaction was positive in nearly all of the patients with fatal or chronic hepatitis and cirrhosis but was not invariably related to the albumin/globulin ratio or globulin content Serum phosphatase concentrations varied too much to be of diagnostic aid

The authors conclude that an albumin globulin ratio below 0 9 and especially below 0 8 in a jaundiced patient practically establishes the diagnosis of chronic hepatitis or cirrhosis This differentiation may be of great help in chronically jaundiced patients for whom surgery is contemplated

Effect of Spontaneous and Artificially Induced Fever on Liver Function During army experience Myers H Hicks Howard P Holt John L Guerrant and Byrd S Leavell[6] (Univ of Virginia) observed that abnormal re

(6) L Cl I t g ti 27 580 587 S pt mb 1948

sults in several liver function tests occurred frequently in conditions other than infectious hepatitis This suggested the importance of studying the effect of artificially induced fever on liver function

Study of 100 patients with atypical pneumonia 100 with tertian malaria and 51 with miscellaneous conditions (but no history of jaundice malaria infectious mononucleosis and pneumonia) revealed *no* correlation between the amount of fever and results of cephalin cholesterol flocculation tests In the same patients however incidence of abnormal bromsulfalein retention was much higher on days when fever was present An unexplained but interesting observation was that the highest incidence of abnormal cephalin cholesterol flocculation reactions among patients with atypical pneumonia occurred during convalescence in the postfebrile period

In 12 patients without fever fever was artificially induced by intravenous injection of killed typhoid organisms and bromsulfalein clearance cephalin cholesterol flocculation prothrombin time total plasma protein level icterus index plasma bilirubin level hematocrit index erythrocyte count and hemoglobin level were determined Only the bromsulfalein test showed significant variation In each subject percentage of dye retention was greater during fever than in the control period In about half the subjects bromsulfalein clearance was still impaired 24 hours after fever subsided When aminopyrine which prevents febrile response to foreign protein injection but does not prevent increase in blood flow to kidney and liver was administered to eight patients before injection of foreign protein no significant impairment of bromsulfalein clearance was observed For these reasons it appears probable that diminished bromsulfalein clearance in the presence of fever is due to impaired function of liver cells rather than to a change in hepatic circulation The authors conclude that temperature of the patient at the time the test is performed must be considered in interpretation of the bromsulfalein test

Turbidimetric Estimation of Serum Colloids in Differential Diagnosis of Hepatobiliary Disease Investigation by Frank T Maher Albert M Snell and Frank D Mann[7] (Mayo Clinic) showed that turbidimetric estimation of gamma globulin is useful in differential diagnosis of hepatobiliary disease Upper limits of normal for gamma globulin turbidity and thymol turbidity were 16 6 and 3 5 units respectively They were selected by adding

SUMMARY OF GENERAL LABORATORY DATA ON PATIENT GROUPS

T s A R su	I c T OU HEPA	HEP TIC CIR H	CHO	O UCTIVE J U CE	
				M l g n t	B gn
Sulfobromophthalein		15	12		
Retention over grade 2		8	2		
Cephalin-cholesterol flocculation	6	11	3	6	16
Flocculation over 2+	5	8	1	0	0
Prothrombin time	15	26	15	11	44
Elevated	9	19	7	2	3
Sedimentation rate	8	11	22	11	26
Elevated	7	2	14	10	25
Total cholesterol	9	16	9	10	22
Increased			1	7	
Decreased	6	3	2		3
Cholesterol esters	9	16	9	10	22
Increased			1		
Decreased	6	8	2	5	5
Serum globulin	10	21*		7	38†
Over 3 0 Gm /100 cc	8	18		0	5†

I 3 f ci h wh h t t f rum gl b l w d 3 0 Gm /100 t h d m t ic l f gamm gl bulin n rum w ormal

†I 5 se f ob truct j d wh h co cent t on f rum gl b 1 w ov 3 0 Gm /100 turb d m t l f g mm gl b l n w m l

twice the standard deviation to the mean values about 11 and slightly less than 2 units respectively for 236 blood bank donors Because of variability of barium sulfate precipitation individual normal ranges should be established in each laboratory using the turbidity procedures

High percentages of positive values for both gamma globulin turbidity and thymol turbidity were found in

[7] Ga oe t logy 12 394 408 M h 1949

infectious hepatitis and hepatic cirrhosis In sharp contrast most values in cholecystitis and obstructive jaundice were within the upper limits of normal The gamma globulin turbidity test has somewhat greater diagnostic efficiency than the thymol turbidity test in differentiating intrahepatic from posthepatic disease Values for both gamma globulin and thymol turbidity are somewhat lower and more variable in alcoholic cirrhosis than in cirrhosis due to other causes General laboratory data on the patients studied are summarized in the table In addition to its diagnostic usefulness the gamma globulin turbidity test is simple and employs a stable conveniently reproducible reagent buffer

Kunkel s turbidimetric method for determining serum lipids showed considerable variation within the several groups of patients studied and results were 10 15 per cent higher than those obtained by chemical analysis of the same serums Values for total lipids were high in obstructive jaundice

Association of Hepatic Insufficiency with Chronic Ulcerative Colitis H Marvin Pollard and Malcolm Block[8] (Univ of Michigan) state that in 87 cases 62 serum protein 27 prothrombin time 27 bromsulfalein and 12 cephalin cholesterol flocculation tests were carried out In 21 cases two or more different liver function tests were performed Results were abnormal in 43 per cent of serum albumin 51 per cent of prothrombin time 44 per cent of bromsulfalein and 50 per cent of cephalin cholesterol flocculation tests When both bromsulfalein and cephalin cholesterol flocculation tests were performed results agreed as to the presence or absence of hepatic insufficiency a fact suggesting that they best reflect the functional capacity of the liver in ulcerative colitis Determinations of total serum protein and prothrombin time were of somewhat less value

Autopsy records in 17 fatal cases of chronic ulcerative colitis were studied Symptoms had been present one month to six years Definite cirrhotic changes were seen

(8) Arch I t M d 8 159 174 A g st 1948

in two and in all others there was either fatty infiltration or degenerative fatty infiltration or both Degenerative fatty infiltration indicates inability of hepatic cells to handle lipids normally and was reflected in diminished liver function as detected by clinical and laboratory means Fatty changes in the liver are caused by severe malnutrition or toxemia or both associated with ulcerative colitis

Validity of Laboratory Evidence in Diagnosis of Sequelae of Acute Hepatitis Henry J Tumen and Edwin M Cohn[9] (Philadelphia) studied 21 patients who had had acute hepatitis 6 months to 10 years previously Five had symptoms possibly attributable to continuing or recurring liver disease and seven had hepatomegaly There was no consistent relationship between these findings and results of laboratory tests

All patients with increased serum bilirubin values gave abnormal responses to one or more liver function tests Serum bilirubin elevations even though slight have diagnostic significance in patients who have had hepatitis and may be regarded as an indication for study

Bromsulfalein retention occurred in 14 patients was occasionally the sole evidence of hepatic dysfunction and with hyperbilirubinemia was the most frequent laboratory abnormality No relation was found between degree of retention residual liver damage and bilirubinemia Absence of abnormal bromsulfalein retention does not exclude residual liver damage

Flocculation tests were rarely positive and were of little diagnostic assistance Residual hepatic damage may be present while such tests are negative

Eight patients had a low prothrombin level and in five this was the most striking abnormality observed Results of other liver function tests were abnormal in all but in some abnormalities were slight Further evidence of hepatic dysfunction was the difficulty encountered in elevating blood prothrombin time with large doses of vitamin K

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(9) G t t l gy 12 9 107 J y 1949

Ten patients had hypercholesteremia It was frequently associated with bromsulfalein retention decreased serum bilirubin level and lowered prothrombin time Hypercholesteremia has many causes but its presence with other laboratory evidence of liver disease requires further investigation

There was no constant relation between results of various laboratory procedures and presence or absence of clinical features suggesting liver disease This supports the opinion that hepatic disturbances may exist for long periods without definite symptoms Prognostic significance of abnormal laboratory findings can be determined only by repeated studies

[This contribution seems noteworthy in one particular despite the small series of 21 cases studied. I have reference to the authors observations on hypoprothrombinemia in eight patients in five of whom this was the most striking abnormality observed That this was due to hepatic dysfunction was shown by marked difficulty in elevating the blood prothrombin by administration of large doses of vitamin K The authors point out that there has been little discussion in the literature concerning the incidence of hypothrombinemia as a sequel to hepatitis Their observation is all the more intriguing because one eminent authority in the field of liver function tests believes that determination of the prothrombin level in the blood is one of the least sensitive tests especially in the earlier stages of hepatic disease —Ed]

Studies on Patients with Cirrhosis of Liver Plasma and Liver Lipid Distribution and Its Relation to Pathology of Liver *George H Stueck Jr Saul H Rubin* Delphine H Clarke Irving Graef and Elaine P Ralli[1] (New York Univ) made pre and postmortem studies of plasma and liver lipids on 21 patients 19 of whom had cirrhosis of the liver Of the 19 16 had ascites 15 were jaundiced and all but 1 gave histories of alcoholism extending over years

Results showed that *there is no absolute correlation* between the amount of total fatty acids in the plasma and in the liver Repeated fractionations of plasma lipids in six cases disclosed that once the liver is severely damaged alterations in plasma lipid fractions remain relatively constant

(1) Am J Med. 5 188 201 A gust 1948

The most reliable index to the pathologic state of the liver is the ratio of free to total cholesterol in the plasma In all patients with cirrhosis this ratio was inverted regardless of the amount of total cholesterol With two exceptions cholesterol fraction was elevated when the other lipid fractions were elevated There were seven patients with elevated total plasma lipids and in three of these the liver lipids were greatly increased

Neither vitamin A nor carotene levels in either plasma or livers bore any relationship to the concentration or distribution of the fatty acids Although the metabolism of these substances is disturbed profoundly in patients with cirrhosis the mechanism of this disorder is probably not the same as that which controls fatty acid disturbance

Liver Function in Chronic Alcoholic Patients Incidence of Liver Disease as Indicated by Laboratory Methods and Suggested Screening Procedure Walter L Voegtlin William R Broz and Marjorie H Moss (Seattle) performed liver function tests on 265 male and 35 female chronic alcoholics (average age 42 8) all of whom were from middle and upper classes of society none being destitute or showing evidences of alcoholic deterioration The table shows the number of patients and percentage of tests positive in each classification of liver dysfunction the 4 plus group representing those with severe liver function derangement and obvious jaundice Abnormal total bilirubin values occurred more frequently than elevation of one minute bilirubin fraction as would be expected in nonobstructive liver disease Positive metabolic and flocculation tests are not characteristic of the type of liver damage found in chronic alcoholics from better classe of society In patients of this type bromsulfalein retention total serum bilirubin and 24 hour quantitative urinary urobilinogen are the most sensitive and reliable tests for detection of liver dysfunction Used as a screening procedure they detect at least 98 8 per cent of patients with slight de

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PERCENTAGE OF TESTS POSITIVE IN EACH CLASSIFICATION OF LIVER DYSFUNCTION

Tests	Classification of Liver Dysfunction					
	0	±	+	++	+++	++++
	No. of Patients					
	9	49	160	5	6	4
Bilirubin 1 min	0	2	15	27	50	100
Bilirubin total	0	33	62	73	67	100
Cholesterol total	0	0	0	0	0	0
Cholesterol esters	0	0	0	0	0	25
Protein total	0	0	0	0	0	66
Serum albumin	0	0	0	0	0	66
Serum globulin	0	0	0	0	0	66
Prothrombin time	14	1	10	41	25	100
Alkaline phosphatase	0	25	44	69	25	100
Cephalin flocc (24 hr)	0	0	1	6	0	25
Cephalin flocc (48 hr)	0	0	1	6	0	25
Thymol turbidity	0	0	1	2	0	0
Thymol flocc	0	0	3	0	0	0
Urinary urobilinogen	0	16	35	52	100	100
Bromsulfalein retention	0	35	76	89	100	100
Hippuric acid synthesis	0	0	8	14	20	50
Galactose tolerance	0	0	2	2	0	0

grees and all with severe grades of liver damage

It is concluded that the type of hepatic dysfunction accompanying chronic alcoholism is probably fatty degeneration of the liver rather than portal cirrhosis With proper treatment it is largely reversible

[Certainly the economic status and by implication the nutritional state of the patient has a direct bearing on the nature and extent of the pathologic process and prognosis The same applies perhaps even more so to ulcer bearing patients —Ed]

Biopsy Investigations of Acute Infectious Hepatitis Aminta Fieschi and Pier Costanzo Curti[3] (Univ of Pavia) studied material obtained by liver puncture in 24 cases The histopathologic picture was characterized by (1) changes of the parenchymatous cells which ranged from albuminoid and vacuolar degeneration to necrosis of colliquative type (2) vasculomesenchymal changes manifested by congestion of blood vessels with hemorrhages thickening of capillary walls interstitial edema

(3) Ga t oe t Ig 74 1 4 1948

sometimes with aspects suggesting serous inflammation and productive reaction of the reticulohistiocytary system with intralobular and interlobular infiltration The picture of acute yellow atrophy of the liver was observed in one case Amount of biliary pigment in the hepatic cells was never above normal Bile plugs were often observed in biliary capillaries

These degenerative and inflammatory changes were variously associated in each case the exudative and degenerative phenomena predominating in some and being more frequent in the first phase of the disease and the productive reticulohistiocytary phenomena predominating in others and being more frequent late in the disease

Liver glycogen was decreased in two patients with severe damage to the hepatic parenchyma Amount of fats was considerably below normal small foci of steatosis were found in only two cases Vitamin A content was also greatly decreased The amount of iron was not uniform but seemed below normal

Codehydrogenase rate was decidedly below normal whereas catheptin activity and oxygen consumption in vitro were increased

In cases in which biopsy was repeated during convalescence normal structure of the liver was almost completely restored

Clinical and Biopsy Study of Acute Dystrophy of Liver Nodular Atrophy and Hepatic Coma after Epidemic Hepatitis Heinz Kalk[4] (Berlin) believes that acute yellow atrophy of the liver and hepatic cirrhosis may be the end result of a single disease The nature of the initial attack determines the course if onset is sudden and the disease severe necrosis occurs with yellow atrophy if the disease is more moderate and develops gradually cirrhotic lesions are formed Epidemic hepatitis causes acute yellow atrophy it may lead directly to death to development of nodular atrophy (potato liver) or to nodular liver with chronic inflammatory reaction This last condition eventually leads to cirrhosis

(4) D tsch m d W h h 73 379 39 S pt mt 1948

with a poor prognosis The potato liver type of change may also lead directly to liver decompensation but may be succeeded by compensation with a good prognosis The clinical sign of acute necrosis of the liver is hepatic coma (with its associated ill smelling odor on expiration)

The type of liver disease can be better determined from laparoscopy and liver biopsy than from the functional tests

The observation that despite destruction of a great portion of liver parenchyma there may be intense icterus indicates that at least a part of the process is extrahepatic Experimentally at least it is possible to separate an indirectly reacting bilirubin from serum albumin by injection of bile acids intravenously

Six cases of severe hepatitis leading to acute yellow atrophy nodular atrophy and cirrhosis are reported Two patients had diabetes one had untreated syphilis one had been given two courses of arsenicals for syphilis and one had severe hunger edema with cholelithiasis

Treatment of epidemic hepatitis should begin with complete bed rest as soon as icterus is found for it has been seen that sequelae are much worse if the patient continues to work or move about Use of an indwelling duodenal tube is the second important measure its primary function is to drain off the poisonous materials elaborated by the injured liver Secondarily it may be used to administer several liters of 5 per cent glucose daily Larger quantities are not advisable

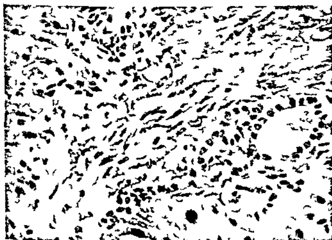
[The observations and convictions of foreign authorities concerning a disease of current concern even if not in strict conformity with our own viewpoints are always interesting and instructive Hence the selection of this and the preceding article —Ed]

Needle Biopsy of Liver James H Topp M C F Lindert and Francis D Murphy[5] (Milwaukee) evaluated 111 Vim Silverman needle biopsies of liver in 100 patients Insufficient or no tissue was obtained in 12 6 per cent but 87 4 per cent were successful No deaths were at

(5) A h Int M d 81 83 858 Ju 1948

tributable to the procedure Slight to moderate bleeding followed withdrawal of the needle in three instances but responded to conservative treatment About 25 per cent of patients complained of pain or vague abdominal discomfort during or shortly after biopsy it lasted an hour or two in all but four in whom it persisted three to nine days

On the basis of degree and type of hepatic cell abnor



Fg 125—E ly p t l h f l (C t y f T pp J H t l A h I t M d 81 83 858 J 1948)

mality and amount of fibrous tissue proliferation portal cirrhosis could be classified into early (Fig 125) moderate and advanced types Other conditions such as hemochromatosis and metastatic adenocarcinoma or melanosarcoma could be recognized microscopically although specimens were 10 20 mm long and about 2 mm wide Biopsies were diagnostically helpful in 86 per cent of cases and in comparison with autopsy specimens the majority were representative of changes in the entire liver

Needle biopsy offers the advantage of following prog

ress of pathologic changes and of evaluating effects of treatment Since autolysis is minimal the tissue for cytologic study is superior Clinical impressions may be confirmed or unsuspected lesions revealed Disadvantages include specimen size likelihood of missing a focal lesion by random sampling and the possibility of complications

The intercostal approach is dangerous because the needle is held firmly betwen the ribs and a liver tear may result if the patient is unable to hold his breath throughout the procedure In addition this approach exposes the pleural sac to danger of infection Biopsy should not be done in the gallbladder region and is precluded by severe ascites and abdominal distention secondary to ileus Liver biopsy should be performed from a subcostal approach only and the liver be palpated at least 4 cm below the thoracic cage Perforation or introduction of infection into other viscera may occur Precautions include determination of bleeding clotting and prothrombin times especially in jaundiced patients Vitamin K should be given when indicated and prothrombin time checked before biopsy

In this series results of hepatic function tests could not be correlated with histologic observations

[Owing to the current widespread interest in this procedure I requested one of my junior associates Dr Stauffer who recently reported on a series of 100 cases (unpublished) to comment in both a specific and a general way

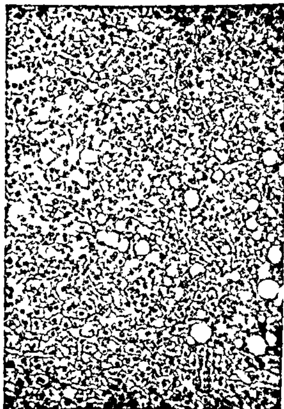
My chief criticism of the foregoing article is the condemnation of the *intercostal approach which seems unjustifiable The series* reported by Cogswell Schiff and their associates (J A M A 140 385 390 May 28 1949) and by Volwiler and Jones (New England J Med 237 651 656 Oct 30 1947) were largely concerned with the intercostal approach Haex of Holland who claims to have done 1 400 punch biopsies is very emphatic about the advantages of the intercostal approach, and believes that the risk of injury to the gallbladder colon or other abdominal viscera is too great when the abdominal approach is used It is true that there have been more deaths following the intercostal procedure but it is *to* be remembered that in the great majority of patients this method was used. Some of the deaths occurred during the early period 1939 44 when proper selection of patients was not made and vitamin K not always utilized. If one is limited to [illegible] abdominal approach one is prevented from carrying out [illegible] many

instances because the liver may be decreased in size in both hepatitis and cirrhosis The intercostal approach is frequently ideal when the liver is pushed up against the chest wall as the result of ascites thus minimizing the hazard of injury to bowel which is not superimposed in such circumstances Too in the occasional presence of slight to moderate distention or tympany in the right upper quadrant it may seem best to use the intercostal approach Moreover some of the earlier deaths were mainly in cases in which the Iversen Roholm needle was used To withdraw the stilet apply syringe and advance the needle is a much longer procedure than that using the Vim Silverman needle which consists essentially of two brief maneuvers Thus the risk from breathing during the procedure and consequent injury is greatly reduced Note that there was no serious reaction to 403 biopsies on 345 patients according to Cogswell Schiff *et al* and the transpleural route was used 378 times My rule is to use the intercostal approach in cases of normal size or barely palpable livers and the subcostal or abdominal one in cases of enlarged livers The abdominal procedure does obviate the possibility of thoracic complications and anesthesia probably is more easily effected Complications following punch biopsy are minimized by proper selection of patient and procedure estimation of prothrombin time (upper limit 24 seconds—Quick) ready availability of transfusion facilities cooperation and at least semi alertness of the patient with the intercostal approach and personal supervision of the patient for at least 24 hours after biopsy

Workers in this field are aware of the not infrequent difficulty of proper histopathologic diagnosis even when successive specimens are obtained from a representative area Further comment by my colleague in this respect may be of interest In general the histologic diagnosis of liver disease is very difficult and in particular the diagnosis of hepatitis There probably is a mild form of viral hepatitis in which the changes are minimal perhaps no more than would be seen in a normal liver The same applies to mild cases of obstructive jaundice The more advanced the process the easier the diagnosis I think that hepatitis should be divided into two forms primary (viral) and secondary i e hepatitis the result of or associated with cholecystitis pancreatitis ulcerative colitis etc Differentiation of these types is difficult There is a conspicuous paucity of cases of hepatitis only one being mentioned in the report by Topp and his associates With respect to cirrhosis it is exceedingly difficult to differentiate between portal biliary toxic and cardiac cirrhosis It is generally agreed that there must be three criteria for the diagnosis of cirrhosis (1) nodular regeneration (2) fibrous tissue hyperplasia and (3) some tissue degeneration or destruction The diagnosis of metastatic carcinoma is usually definitive although difficulty has been encountered because the centers of the tumors often are necrotic resulting in degeneration of the cells to the extent that their identification is problematic —Ed]

Combined Liver Biopsy and Liver Function Study in 132 Cases of Cholelithiasis and 31 Cases of Peptic Ulcer (O — Cases) is reported by John G Mateer Frank

W Hartman James I Baltz Laurence D Fallis Arthur B McGraw and Hugh H Steele[6] (Henry Ford Hosp) with emphasis on early microscopic liver disease and particularly acute infiltrative hepatitis and microscopic



F g 1 6—Acut filt t h p t t d ff se polym ph n cl filt t on w th fatty ch ge f cell but n crosis M d m pow r

periportal cirrhosis Of the 163 patients 121 showed no alteration in size of the liver jaundice or other clinical evidence of liver disease As soon as the abdomen was opened at laparotomy liver biopsies were obtained from

(6) Ga t oe t ology 11 284 30 Sept mbe 19

the right lobe of the liver far distant from the attachment of the gallbladder Wedge biopsies were obtained from all 163 patients and needle biopsies from 55 Though livers were grossly normal when viewed at operation in all patients only 6 per cent of the 132 with gallstones and 7 per cent of the 31 with ulcers had histologically normal livers

Two microscopic conditions of particular interest were found *microscopic periportal cirrhosis and acute infiltrative hepatitis* The former condition characterized by a slight abnormal increase in fibrous stroma and by mononuclear infiltration of the stroma was found in 33 per cent of the patients with gallstone and in 29 per cent of those with peptic ulcer Acute infiltrative hepatitis was characterized by extensive and diffuse polymorphonuclear infiltration with vacuolar degeneration of the liver and absence of necrosis (Fig 126) This condition has not previously been emphasized in the literature It was found in 15 per cent of the patients with gallstones and in 10 per cent of those with peptic ulcer Liver changes in these patients were attributed to inflammation in the gallbladder and about the base of ulcers

More than half the patients with gallstones had bile staining of liver parenchymal cells vacuolation or fatty infiltration and 92 per cent had some abnormal thickening of the stroma Six types of liver function tests were used The bromsulfalein test was positive in over a third of each of the two groups and the other tests were positive in over 10 per cent of each group Tests were usually only slightly but definitely positive Patients with parenchymal liver damage had the greatest percentage of positive tests However no deduction regarding the parenchyma could be drawn from a positive test since an appreciable number of positive tests were associated with structurally normal parenchymal cells The authors regard liver function tests and liver biopsies as separate items of diagnostic information with different relative value in different types of disease

[This is essentially a study of very early acute and chronic liver

disease by experienced workers under fairly ideal conditions and comprised of material of sufficient proportion to add to the statistical value and reliability of the investigation Although we have long been cognizant of hepatic changes in association with cholecystic disease and chronic peptic ulcer so that occasionally one couldn t tell which was the egg and which the hen one is impressed with the high percentage of histologic changes in the liver and their nature as indicated by this study The relatively high incidence of one or more positive results of liver function tests of course is explained by the fact that multiple tests were employed including four of the most sensitive ones The authors commendably point out that information regarding liver function and biopsy evidence regarding liver morphology must be considered more or less as separate items of valued diagnostic information —Ed 1

Treatment of Hepatic Amebiasis with Chloroquine Neal J Conan Jr[7] (Columbia Univ) studied seven patients with amebic hepatitis each of whom was successfully treated with chloroquine Extensive localization of this drug in liver (some 500 times its plasma concentration) occurring in many animals and presumably in man a three to fourfold lesser degree of localization in intestinal walls and its almost complete absorption from the gastrointestinal tract have made it seem ideal for treatment of this disease

Although the etiologic agent was not isolated from the involved organ Endamoeba histolytica was the only organism found in these patients that is known to infect liver In each patient hepatitis began to clear one or two days following institution of therapy and progressively improved without recurrence

The dosage is 1 0 Gm chloroquine diphosphate daily for two days *followed by 0 5 Gm daily for two to three weeks*

Chloroquine causes only minor toxic manifestations Among 40 patients treated for amebiasis 3 complained of nausea 1 of transient pruritus and 1 of disturbed ocular accommodation but it was never necessary to discontinue or interrupt medication It does not have the serious toxic potentialities of emetine does not require parenteral administration and is more uniformly effective in treatment of amebic hepatitis or liver abscess

Because of the high frequency of metastatic infection

(7) Am J M d 6 309 3 0 Ma h 1949

and the impossibility of determining whether extraintestinal involvement has occurred it is desirable to treat every patient with intestinal amebiasis with agents which eradicate amebas wherever they are Since chloroquine is *only about 50 per cent curative for intestinal amebiasis* it should be used in conjunction with a more efficient intestinal amebacide for all patients with the disease In treating hepatic amebiasis even without signs of intestinal involvement an intestinal amebacide should be used in addition to chloroquine so that colonic foci of infection may be more certainly eradicated

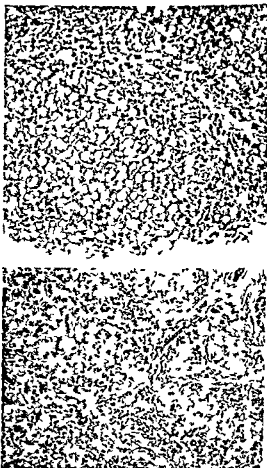
[A circumspect perusal of the case reports leaves no doubt of the effectiveness of chloroquine in the treatment of hepatic amebiasis As a substitute for the more toxic emetine with its inconvenient mode of administration it appears to be full of promise —Ed]

Criteria for Measurement of Results of Treatment in Fatty Cirrhosis Wade Volwiler Chester M Jones and Tracy B Mallory[8] (Harvard Univ) performed punch biopsies of the liver before and after approximately 30 days of treatment in 13 patients with alcoholic cirrhosis Except in a few cases bromsulfalein tests serum albumin determinations and cephalin flocculation tests were done before and after treatment No two patients were given the same treatment Fat content of the diet varied from 30 to 220 Gm daily protein content from 120 to 195 Gm and caloric intake from 1 600 to 4 000 Dietary supplements consisting of choline inositol yeast liver extract and/or vitamins were given to nine patients

Except in rare instances biopsies showed less necrosis and fat after treatment than before (Figs 127 and 128) There was little change in the amount of fibrosis in the liver Most patients retained less bromsulfalein and had higher concentrations of serum albumin after treatment than before but cephalin cholesterol tests gave little indication of improvement in liver function

Since there was no clinical or laboratory evidence to suggest that the patients given dietary supplements got along better than the four not so treated the authors

(8) G t t l gy 11 164 18 A g t 1948



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(Cou t y of Volw l r W *et l* C t oent l gy 11 164 18 A gu t 1948)

are convinced that addition of lipotropes and/or vitamins to an adequate diet is unnecessary in such cases High fat intake seemed compatible with improvement in pa tients with fatty cirrhosis on otherwise adequate diets

The authors agree with others that lipotro es or vita

mins are not substitutes for an adequate diet and that moderate alcohol intake does not prevent improvement in adequately nourished patients with fatty cirrhosis

[The results of this investigation further justify the present tendency to add moderate or liberal amounts of fat to the diet in the treatment of acute and chronic hepatitis and the impression of highly probable superfluity of lipotropic agents in the prophylaxis and treatment of the fatty and chronic forms of hepatic cirrhosis —Ed.]

Correlation between Cholecystogram and Secretin Test for Gallbladder Function. The property of secretin (a hormone produced by the small intestine) to stimulate flow of liver bile as well as pancreatic juice has been utilized as a test of gallbladder function In the normal subject the increased amount of bile secreted by the liver after secretin administration is taken up by the gall bladder where it is subjected to concentration After secretin injection duodenal content thus consists mainly of pancreatic juice and occasionally some bile Icterus index curve of the duodenal content shows only an occasional high point In persons with cholecystectomy storage space for secretin stimulated liver bile is absent and consequently bile flows directly into the intestine so that all duodenal content samples consist of pancreatic juice with a high color index In the patient with a nonfunctioning gallbladder the condition is essentially similar to that in the cholecystectomy patient in that secretin stimulated liver bile enters directly into the duodenum

W J Snape M H F Friedman and P C Swenson[9] (Jefferson Med College) performed cholecystographic and *secretin tests of gallbladder function on 64 patients* most of whom had some form of gastrointestinal disease Results of the two tests agreed in 55 patients In nine results of the secretin test disagreed with the cholecystographic picture In two of these the secretin test and subsequent autopsy both revealed the gallbladder to be normal but the cholecystogram suggested a nonfunctioning organ In the other seven patients it was the secretin test that indicated the gallbladder to be non

(9) Am J M S 16 189 194 A gu t 1948

functioning In two of these seven patients the gall bladder while visualized was seen to contain calculi

The secretin test showed a high degree of correlation with clinical diagnoses This test is not suggested as a substitute for the much simpler procedure of cholecystography However it is possible that in some cases a gallbladder with only slight impairment in concentrating functions may during the 15 18 hours between ingestion of dye and x ray study concentrate sufficient radiopaque dye to make it visible and yet not remove enough liver bile during the one hour secretin test to alter appreciably the duodenal bile pigment index The authors suggest that the secretin test is a useful *supplement to the usual procedures and recommend it when data from the cholecystogram are difficult to interpret*

Studies on Carbohydrate Metabolism and Liver Protection Therapy in Experimental Extrahepatic Biliary Obstruction. Yngve Edlund[1] produced total biliary stasis in 111 rats by ligation and cutting of the common bile duct and partial biliary stasis in 18 rats by ligating this duct with heavy catgut Rats with total biliary stasis were killed and examined 1 to 34 days after operation those with partial biliary stasis 12 and 34 days after operation

In animals with total biliary stasis abundant necrosis of liver cells especially in the peripheral parts of lobules appeared in the first four postoperative days Afterward the amount of necrosis decreased Accumulation of toxic bile acids in liver cells was possibly responsible for early destruction of the cells whereas later destruction was caused by *invasion of bile ducts into lobules and severing of liver cell connections due to pressure increase in bile canaliculi* Proliferation of bile ducts and dilatation of bile canaliculi were very intense 24 34 days after operation causing complete destruction of lobular architecture In addition to liver changes animals with total biliary stasis of long duration (24 and 34 days) exhibited degenerative changes in the epithelium of renal tubules

(1) Acta h Scandin pp 136 v 1 96 1

Animals with partial biliary stasis showed no necrosis in liver cells There were increase of bile ducts in portal spaces and slight invasion of bile ducts into lobules but in general histolo ic structure was well preserved

Serum bilirubin in rats with total biliary obstruction increased within 15 minutes after ligation and cutting of the common bile duct Bilirubin content reached its maxi mum after eight days of biliary stasis then declined gradually In the beginning hyperbilirubinemia in acute obstruction of the common bile duct is cau ed by a changed secretion mechanism in liver cells with empty ing of bilirubin toward lymph and blood vessels In later stages bilirubin retention is probably present caused by decrease or cessation of the secretory function of liver cells possibly combined to some extent with passing of bilirubin from bile canaliculi toward lymph and blood vessels Some retention may be present in early stages also caused by a relative blocking of liver and Kupf fer cells

Biochemical investigation of carbohydrate metabo lism in total biliary stasis revealed a great decrease in the glycogen in the liver and musculature The longer the duration of biliary stasis the less was the glycogen content of the liver Blood sugar levels also decreased probably because of the low glycogen content Hyper ketonemia was found with considerable increase in the β hydroxybutyric acid content of the blood However the β hydroxybutyric acid level decreased in long stand ing biliary stasis presumably due to decreased produc tion in the liver as a consequence of the severe hepatic lesion In partial biliary stasis the glycogen content of the liver and musculature was not decreased 12 days after operation

Many different experiments were carried out to deter mine the cause of the low glycogen content in total bili ary stasis Edlund concludes that a disturbance of the glycogen storing function of the liver is present caused by disturbed glycogenesis and increased glycogenolysis The essential disturbance was considered to be decreased

formation of phosphate bound energy caused by dis turbed metabolism in the isocritic acid cycle possibly with blocking between fumaric acid and succinic acid These metabolic disturbances are probably started by accumulation of bile acids in liver cells The increased glycogenolysis may be caused by increase of the amount of inorganic phosphate decrease in pH or possibly in creased amylase activity In later stages of biliary stasis the low glycogen content of the liver probably results from the general functional disturbance caused by de crease in parenchymal cells and damage to the remaining cells

Parenteral administration of large doses of glucose adenosine triphosphate or fumaric acid increased the liver glycogen content in these animals Secondary in crease in blood sugar levels and decrease in blood β hy droxybutyric acid content were also observed Parenteral administration of amino acids insulin or B complex vitamins together with glucose seemed to counteract the glycogenetic effect of glucose in liver and musculature Addition of amino acids and glucose to ordinary food with or without addition of bile acids did not increase the glycogen content of liver and musculature and did not normalize blood sugar and blood ketone levels

No form of liver protection therapy even though it increased liver glycogen content prevented appearance of histologic dama e Neither enteral nor parenteral ad ministration of amino acids glucose or methionine had any effect on the structural liver damage produced by ligation and cutting of the common bile duct However it is considered important in total biliary stasis to use a therapy which increases the glycogen content in the liver even though hepatic lesions cannot be prevented The glycogen thus supplied gives the liver an energy source for its vital functions

Silent Gallstone Mandred W Comfort Howard K Gray (Mayo Clinic) and James M Wilson* (Mayo Found) report 10 20 year follow up in 112 cases in

( ) A n S g 128 931 937 N mber 194

which asymptomatic gallstones were found incidentally during an abdominal operation In 30 cases indigestion developed 21 patients reported colic and 5 had both colic and jaundice The others remained asymptomatic

Cholecystectomy was performed on 24 of the patients with symptoms Three died postoperatively In the entire series 25 other patients died As far as can be ascertained 21 did not experience symptoms before death In none was the cause of death related to gallbladder disease

It is concluded that surgical treatment of the silent gallstone may be classified as optional or elective Surgery should not be postponed after symptoms develop and especially after attacks of colic appear By refusing elective surgery the patient accepts the chance of experiencing painful seizures and the increased risk of surgical treatment should complications of calculus disease of the biliary tract appear

[An instructive contribution to a subject of great practical import —Ed]

Value of Duodenal Drainage Its Place in Diagnosis is discussed by S Allen Wilkinson[3] In 15 years duodenal drainage studies have been done over 1 000 times at Lahey Clinic Accuracy of interpretation of these tests cannot be verified in all instances because in many cases surgery was not done However follow up indicates that diagnoses were accurate in most cases Among patients operated on accuracy of diagnosis was 94 per cent A normal biliary tract was found in 531 patients Biliary tract infection without stones was diagnosed 226 times common duct stone 237 and malignancy 6

Duodenal drainage is recommended when diagnosis of gallbladder disease is doubtful despite repeated Graham tests There are few such cases because nearly always repetition of the Graham test after four to six weeks of strict dietary regulation reveals a functioning normal gallbladder or a nonfunctioning abnormal organ Little more can be gained by using duodenal drainage In pa

(3) S Cl North Am 28 587 591 J 1948

tients with common duct stone whose gallbladders have been removed nothing can replace duodenal drainage It has been shown repeatedly that x rays will not reveal these stones Drainage is of value in diagnosis of cholangitis revealing pus cells bacteria and tall columnar epithelial cells of the biliary tract stained with bile It may be used to determine presence or absence of bile in the duodenum of patients with jaundice thought to result from common duct obstruction Obstruction can be assumed to be present if with the tip of the tube in the *duodenum no bile is obtained Malignancy of the head* of the pancreas ampulla of Vater or biliary tree can be assumed to be present if gross blood is found in the duodenal contents and an x ray fails to reveal duodenal ulcer Failure to find gross blood does not rule out malignancy

Duodenal drainage should not be carried out if diagnosis is already established if the patient is very weak or very ill or if operation has already been decided on

TECHNIC —A Rehfuss tube is passed through the mouth and swallowed until its tip reaches the cardiac end of the stomach —usually to the first mark on the tube The patient is then turned on the right side and instructed to swallow tube slowly over 20 minutes to the third mark Thirty cc of 50 per cent magnesium sulfate diluted to 100 cc with warm water is put into tube and the duodenal contents are siphoned back immediately With a pipet flecks which float in bile or form sediment on the bottom of a specimen bottle are withdrawn and placed on a slide for microscopic study

Normal bile is yellow dark brown or mahogany and clear or turbid Bile stained pus cells bacteria or columnar epithelium may be regarded as conclusive evidence of an infectious process of the biliary tree Pus cells or epithelial cells which are not bile stained may have originated elsewhere and have no diagnostic significance If duodenal ulcer has been excluded gross blood or strands of bloody mucus almost always indicate malignancy *Cholesterol* crystals or calcium bilirubin pigment usually indicate stones in the gallbladder or common bile duct Stones were found in 80 per cent of cases in which crystals alone were present in over 90 per cent in which pig

ment alone was present and in about 96 per cent in which both crystals and pigment were present

Duodenal drainage is time consuming and difficult but proper use has saved many patients from operation or has verified diagnosis of stones and indicated necessity of an operation which might otherwise not have been done

[A timely article on a diagnostic procedure too much neglected when the indications for it exist as properly pointed out by the author —Ed]

Effect of Ligation of Pancreatic Ducts and of Pancreatectomy after Duct Ligation on Serum Lipase Martin M Nothman T Dennie Pratt and Joseph Benotti[4] (Boston) found the average serum lipase level in 20 dogs to be 0 6 unit Lowest value was 0 2 and highest values were 1 6 in one dog and 1 1 and 1 2 in three others The pancreatic duct was ligated in all 20 dogs after which the serum lipase content greatly increased in all but 1 dog beginning within 24 hours after operation Serum lipase determinations on six dogs the day after ligation gave values between 3 6 and 7 3 Average amount of serum lipase in these dogs had been 0 4 average amount 24 hours after ligation was 5 1 and on the second day 7 After six or seven days amount of enzyme dropped in some dogs and rose in others in two highest values were found 10 and 22 days after ligation

Increase of serum lipase is apparently due to its absorption into the blood stream when the flow of pancreatic juice has been blocked To substantiate this conclusion the authors ligated the pancreatic ducts of four dogs and drew the tail of the pancreas through the abdominal wall exposing the tip through the skin Serum lipase value rose from 0 4 to 2 units within 48 hours The tip of the exposed gland was then transected thereby permitting pancreatic juice to escape The first lipase determination two days after operation showed lipase to be decreasing and the value returned to normal when the fistula was well established

(4) J Lab & Cl M d 33 833 840 J ly 1948

The authors performed total pancreatectomy alone on three dogs and on five total pancreatectomy was done five to nine days after duct ligation Dogs with pancreatectomy alone showed a steady decrease of serum lipase until death five or six days after operation In the other five serum lipase rose markedly after tying the ducts After removal of the pancreas there was an immediate drop of serum lipase In three animals lipase values were almost zero on the second day after operation In the other two there was an essential but less pronounced decrease in the enzyme These two dogs were still living three and four weeks after pancreatectomy whereas the other three died a few days after operation In the surviving dogs serum lipase levels rose to values above *normal three weeks after operation* The authors conclude that serum lipase originates at least in part in the pancreas The liver is suggested as another possible source

[These experiments have a background of practical import Cherry and Crandall (1932) found an olive oil splitting enzyme in relatively large amounts in the blood of dogs after ligation of the pancreatic ducts This became the basis for the clinical use of the serum lipase test in the diagnosis of pancreatic disease One group of investigators was unable to confirm Cherry and Randall s results Such failure of confirmation would deprive the test of its essential experimental confirmation Happily the investigation reported here and several others verify the original observations —Ed]

Dilatation of Acini of Pancreas Incidence in Various Pathologic States Archie H Baggenstoss[6] (Mayo Clinic) observed this lesion in about 45 per cent of 270 cases of uremia and in about 20 per cent of 200 cases in which death was not due to uremia In the latter group acinar dilatation was most frequently associated with carcinoma of the stomach (Fig 129) small intestinal obstruction (Fig 130) infection (sepsis or septicemia) and chronic ulcerative colitis

The genesis of this lesion is not known A viscid pancreatic juice might become inspissated and obstruct the ductules and acini with resultant dilatation Other pos

(6) A h P th 45 463 473 Ap 1 1948



Fg 129 (top) —D l t t f f p n f g t m H m t yl d d d f m × 110
Fg 130 (bott m) —D l tat f ci f p f b t tion f m ll te t H m t yl n d d d f m × 165
(C te y f B gg t A H A h P th 45 463 473 Ap l 1948)

sible important factors are dehydration and interference with normal release and action of secretin caused by excessive vomiting gastric distention which inhibits pancreatic secretion depletion of zymogen granules by

excess vagus and sympathetic nerve stimulation and failure of reparative protein synthesis of cytoplasm and zymogen granules due to prolonged malnutrition Since many factors probably cause dilatation of pancreatic acini in adults the same may be true regarding fibrocystic disease of the pancreas in children

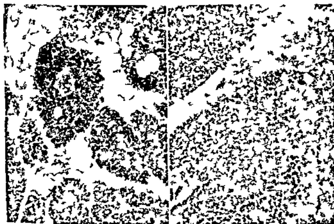
Transition of Pancreatic Edema into Pancreatic Necrosis H L Popper H Necheles and Kemper C Russell[5] (Michael Reese Hosp Chicago) state that in dogs injection of secretin after pancreatic duct ligation produces pancreatic edema but never pancreatitis When the arterial supply of the pancreas is interrupted in the presence of pancreatic edema changes develop which range from a mild form of intraperitoneal fat necrosis to severe hemorrhagic and necrotizing pancreatitis Either the temporary ischemia lowers resistance of the cells to the enzymatic action of the edema or the pancreatic enzymes of the fluid are activated by contact with impaired cells

These experimental observations have several clinical applications (1) Local vasomotor changes may be responsible for transition of pancreatic edema to pancreatic necrosis (2) The extent of local vasomotor changes may determine the degree of pancreatitis (3) If acute pancreatitis is diagnosed or suspected treatment should be directed toward dissipation of the edema and avoidance of local ischemia Use of drugs which will relax the sphincter of Oddi and prevent active inhibition of external secretion of the pancreas may cause edema to disappear Local ischemia may be avoided by preventing shock and omitting medication that has a vasoconstrictor effect in the splanchnic area Papaverine is of value because of its vasodilating effect Paravertebral block may also cause vasodilatation

Etiology of Acute Pancreatitis Experimental Study is reported by Rolf Lium and Stephen Maddock[7] (Tufts College) Their object was first to obstruct the pancreatic ducts and then to stimulate the gland by feeding admin

(5) S g Gy & Ob t 87 9 8 J ly 1948
(7) S g ry 4 593 604 O t b 1948

istration of parasympathomimetic agents such as pilocarpine acetylcholine and eserine or administration of secretin Two sets of experiments were performed with each method of stimulation In one group both greater and lesser pancreatic ducts were located but not tied in the other a silk ligature was placed around both ducts The element of surgical trauma was thus eliminated as a



Fg 131 (l ft) —F t tag f p t fl mm t n w th w d g f l b l pt d m ld d g f cu fl mm t y n t t pt f g n l t d by w wh m d t g t f lobul p t
Fg 132 (ght) —S d d th d t g w th m t t b tw l b l d d t t t l g t l gth f l b l S b ta f l b l b w m fl mm t y ll Sp m f m ta d t g p l ca p n d k ll d 48 hou ft l g t f d t
(C t y f L m R d M ddock S S g y 24 593 604 O t b 1948)

source of pancreatic inflammation Cats were used and were usually killed 24 48 hours after operation

No fat necrosis occurred when simple laparotomy was done with exposure of ducts but without ligation when ducts were tied in starved animals and no stimulant administered or when animals with intact ducts were fed or were given pilocarpine secretin or other stimulants However when ducts were tied and animals fed or stimulants administered gross fat necrosis was found in most

animals and the pancreas on microscopic section showed an inflammatory reaction which varied widely in degree The mildest degree of pancreatitis was characterized by widening of the septa with inflammatory cells and exudate in the septa Pancreatic tissue appeared normal (Fig 131) The next stage showed more extensive inflammation in the septa and beginning invasion of lobules by inflammatory cells (Fig 132) The third stage revealed beginning destruction of acini most pronounced at the periphery of the lobule (Fig 132) and in the last stage the entire lobule was undergoing dissolution Failure to find gangrenous pancreatitis and extensive vascular damage in these animals is attributed to the anatomy of the cat s pancreas

The authors conclude that acute pancreatitis results from ductal obstruction in an actively secreting pancreas

[Those interested in the theories proposed and the investigations carried out in the elucidation of this baffling problem should read the article in its entirety Obviously the authors hold no brief for the common channel theory which has numerous proponents The available evidence which led to the choice of experiments undertaken and the probable factors operative in man whereby the conditions of the experiment are approximated makes for instructive reading whether or not you agree with the investigators postulates —Ed]

Acute Pancreatitis H L Bockus and Edward C Raffensperger[8] (Univ of Pennsylvania) review their experience in 10 cases Important etiologic factors in this condition are excessive use of alcohol and biliary tract disease In the present series the former factor was implicated in four cases the latter in five and both factors in one case

Acute pancreatitis follows no consistent symptom pattern The initial pain is usually in the epigastrium and may radiate to the left and to the area of the first or second vertebra Pancreatitis may simulate rupture and perforation of a hollow viscus or small bowel obstruction The shocklike state seen in some cases in combination with high epigastric substernal or high back pain may suggest acute coronary occlusion Because of these

(8) New York State J Med. 48 5 2 59 Oct 15

similarities bedside diagnosis of acute pancreatitis rarely if ever possible

Serum enzyme tests are of value in establishing di nosis The authors have observed marked hyperenzy emia during the first three days of illness in all cases acute necrosis of the pancreas However absence of creased blood serum enzymes does not exclude the p sibility of pancreatic inflammation The serum amyl test (saccharogenic method of Somogyi is used by authors) has proved of greatest value because it may done within one hour In pancreatitis the level of ser amylase rises earlier than does that of lipase After first 48 hours the serum lipase determination (Loer *hart method as modified by Cherry and Crandall)* the greatest value Concentration of serum lipase rem greater for a longer period than that of serum amyl The authors perform these tests routinely on all pati suspected of having acute cholecystitis or severe bili *colic* on patients with acute severe abdominal pain undetermined origin or severe injury to the abdomen on those admitted in a shocklike state Serum amy concentrations of 500 mg or over are highly suggest if not indicative of primary acute pancreatitis

Hydrolysis of fat by pancreatic enzymes into glyc and fatty acids and the combination of these substa with calcium to form calcium soaps may result in a creased calcium concentration in the blood serum In present series the most seriously ill patients had the l est serum calcium values In two hypocalcemia was ficiently marked to necessitate administration of calc intravenously Appearance of hypocalcemia on fourth day or later may support the diagnosis of a pancreatitis

According to Bellet profound changes occur in electrocardiograms of many patients with acute panc titis Inversion of the T waves in lead I in the o limb leads and in precordial leads accompanied by v ing degrees of depression of the S T segment are s These changes gradually return to normal with impr

ment in the clinical state In conjunction with the clinical picture they might be confused with the findings of acute myocardial infarction

Operation during the acute phase is generally considered unwise For relief of pain demerol® with its atropine like action is the analgesic of choice Use of morphine should be avoided Phenobarbital may be given as needed Paravertebral block on the left side at the level of the eighth to tenth thoracic spinal processes may be considered Shock and dehydration should be vigorously treated Since diabetes mellitus occasionally accompanies acute pancreatic necrosis glucose infusions must be given cautiously and blood sugar determined frequently With occurrence of hyperglycemia 5 10 units of regular insulin should be given subcutaneously with each 25 Gm glucose intravenously Of greater importance is the necessity for avoiding insulin shock and hypoglycemia

Hormonal stimulation of the pancreas should be avoided A nasal tube should be introduced into the stomach with its tip proximal to the pylorus so that gastric juice containing hydrochloric acid does not pass into the duodenum Constant Wangensteen suction should be maintained Soluble or insoluble alkalis are administered every one or two hours during the period of suction Atropine sulfate (1/75 1/150 gr every four hours) is used to depress vagal activity and reduce volume of gastric secretion Ephedrine may inhibit the flow of pancreatic juice *Drugs which stimulate the vagus nerves are to be withheld* If a calcium deficit is detected calcium gluconate should be administered parenterally

[A convincing summary of generally accepted concepts with reference to precipitating and causative factors symptoms sign and treatment in its major aspects of a primary clinical entity or *intercurrent* acute manifestation of a chronic disorder well deserving the appellation abdominal catastrophe —Ed]

Allergic Pancreatitis Pancreatitis due to allergy is either very rare or unrecognized Jane Schaffer[9] reports such a case

(9) P rman t F n1 M B ll 6 204 07 O t be

Man 48 was hospitalized June 3 1947 because of urticaria and abdominal pain for one day The pain was constant severe and cramping and arose in the midepigastrium then passed to the back It was accompanied by nausea and vomiting without diarrhea Intermittent severe attacks of generalized urticaria with or without abdominal pain had occurred for five years In 1943 he had acute pancreatitis confirmed on laparotomy and treated by biliary tract drainage

On admission pulse rate was 140/minute respiratory rate 35 and temperature 101 F The body was covered with giant wheals There was diffuse abdominal tenderness with muscle spasm most prominent in the midepigastrium Leukocyte count was 84 0 with 69 per cent neutrophils Serum amylase value was 300 units and urine amylase value 438 units

Pyribenzamine® 150 mg was given orally at 6 p m the day of admission and 100 mg was given four times daily thereafter Within an hour the abdominal pain and hives began to subside and in three hours he was free from pain and relatively free from hives He remained asymptomatic except for nausea and abdominal distress which was relieved by giving the drug after meals He was discharged the fourth hospital day and remained well On June 9 serum amylase value was 115 units and urine amylase value 140 units

When a patient known to have allergies has gastrointestinal complaints the possibility of allergy must be considered Symptoms caused by allergy may simulate appendicitis biliary colic or intestinal obstruction An excess of eosinophils in mucous discharges and blood is apparently unreliable in diagnosis of specific allergies Gastroscopy and sigmoidoscopy can be used to incriminate definitely suspected food allergens by observing mucosal changes after ingestion or direct application of suspected food X ray examination of the stomach gall bladder and colon using allergen and barium meals has been useful in some cases

I The accuracy with which an unu ual di ord r may be diagnosed depends upon the d gree of suspic on aroused in the clinician This i undoubtedly an unusual manifestation of visceral allergy but there is no reason to believe it cannot occur in view of the protean natu e of allergy The urtica ia associated with the abdominal manifestations is always a diagnostic signpo t and should give pause to any surgeon I have seen instan es of hepatic allergy characteri ed by generalized urticaria vomiting diarrhea general ed abdominal pain followed by cterus and a t nder enlarged

Relief of Pain in Acute Pancreatitis Seibert Pearson and John C Lungren[1] (Long Beach Calif) state that etamon® (tetra ethylammonium chloride) effectively blocks sympathetic and parasympathetic impulses at the ganglionic synapse Because both sympathetic and vagal stimuli incite pancreatic secretion they assumed that the drug would be of benefit in the nonsurgical treatment of acute pancreatitis and used it in one case

Woman 32 was hospitalized at 3 p m February 24 with severe upper abdominal pain nausea and vomiting The pain radiated around both costal borders was viselike and became severe intermittently with a steady pain between paroxysms She had had occasional episodes of similar severe pain for the preceding 10 years Cholecystectomy was done in 1943

The patient was in acute distress restless and groaning in pain with knees drawn up There were marked tenderness and muscle guarding in the epigastric region Temperature was 99 2 F and pulse rate 104 White blood cell count was 14 950 with 80 per cent polymorphonuclear leukocytes Serum amyl ase value at 8 p m was 2 017 mg sugar/100 cc (normal 70 100 Somogyi modified technic) Serum bilirubin level was 1 7 mg /100 cc (normal 0 1 0 8 mg) At 8 45 5 cc etamon® solu tion was administered intravenously Although she complained of numbness in the feet and hands and that her lips felt weak the abdominal pain disappeared while the solution was being injected At 7 a m abdominal pain recurred At 8 15 5 cc etamon® was given intravenously the pain again disappeared immediately but she complained of a tingling sensation in the hands and feet and of some difficulty in focusing her eyes During the next 36 hours 3 cc doses of etamon® were given intramuscularly four times Serum amylase and bilirubin level declined gradually in the three days after admission On March 3 she reported that she had remained well Serum bilirubin level on March 22 was 0 4 mg /100 cc

[This apparently was an instance of acute exacerbation of chronic relapsing pancreatitis It i to be hop d that etamon® will prove as effective in every instance Severe toxic reactions occa sionally occur following its administration so that this possibility must be borne in mind and promptly corrected by the intravenous administration of 0 5 1 0 mg neo tigmine —Ed]

Pancreatic Function as Measured by Analysis of Duo denal Contents before and after Stimulation with Secre tin George R Dornberger (Mayo Found) Mandred W Comfort Eric E Wollaeger (Mayo Cl

(1) A W t Med & S g 2 550 552 D m

schelle H Power (Mayo Found) analyzed the duodenal contents for volume and bicarbonate and enzyme content in 28 cases of proved chronic pancreatitis before and after stimulation with secretin Before secretin stimulation values are not indicative of disturbance of external pancreatic function unless there is almost complete abscence of bicarbonate and of enzymes because values for normal persons lie in a low range

A rough correlation exists beween the degree of pancreatic destruction as judged by clinical course and pathologic findings at operation or necropsy and the result of the secretin test The test demonstrated insufficient external secretion in all cases of pancreatitis with extensive parenchymal destruction as indicated by calcification diabetes and steatorrhea It also disclosed disturbance of external function in over half the cases of chronic pancreatitis without evidence of extensive parenchymal damage

The test gives reliable information only when the strength of the secretin is standard and the duodenal contents have been quantitatively aspirated uncontaminated by acid gastric contents Since total enzyme determinations did not furnish information not given by determinations of volume and bicarbonate and total bicarbonate concentrations it would appear that the last three parts of the secretin test are most useful in evaluating the state of external function of the pancreas An explanation for this lies in the fact that pure secretin is an active stimulant of secretion of water and bicarbonate but merely washes out the enzymes

The test disclosed insufficiency of external secretion more often than did fecal analysis and appeared to be of greater value in diagnosis of chronic pancreatitis This was especially true when diagnostic sequelae of pancreatitis were not present However since the test alone will not distinguish between impaired external function due to pancreatitis and that due to other causes it has a definite but limited place in diagnosis of pancreatitis

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[Authorities differ as to the diagnostic value of this test. For example McDonough and Heffernan in a paper on chronic relapsing pancreatitis in *Surgical Clinics of North America* June 1948 quote Dozzi and Bockus (Bockus H L *Gastro enterology* [Philadelphia W B Saunders Company 1946] Vol III p 758) as follows It seems highly unlikely that any estimation of enzymes in the duodenal fluid in chronic disease of the pancreas will frequently yield information of great diagnostic value which is not suggested by fecal analysis disturbance of COH metabolism roentgen ray study physical examination or serum enzyme tests with the utilization of pancreatic enzymes

In response to my query on this matter Dr Dornberger submitted the following comment The secretin test has a definite but limited place in the diagnosis of chronic relapsing pancreatitis Determinations of total volume concentration of bicarbonate and total bicarbonate are the important parts of the test rather than the values for enzymes Twelve patients with proved chronic relapsing pancreatitis without any of the sequelae such as diabetes steatorrhea or calcification of the pancreas were studied with the secretin test during the interval between attacks when serum enzyme values were normal Presumptively abnormal values for volume and bicarbonate or for bicarbonate alone disclosed disturbance of external pancreatic secretion in 7 of the 12 patients —Ed]

Total Fecal Solids, Fat and Nitrogen Study of Patients with Chronic Relapsing Pancreatitis George R Dornberger (Mayo Found) Mandred W Comfort Eric F Wollae er (Mayo Clinic) and Marschelle H Power[3] (Mayo Found) made intake excretion studies on 10 patients with chronic pancreatitis and sequelae such as diabetes calcification and gross steatorrhea and on 10 patients with chronic pancreatitis but no sequelae Only the differences between the average daily fecal values of total solids fat and nitrogen for a normal group and the group of patients with sequelae were statistically significant Average daily total fecal solids varied from 8 5 to 87 6 Gm (normal limits 13-42 2 Gm) average daily fecal fat from 3 1 to 44 4 Gm (normal 1 1 7 1) and average daily nitrogen from 1 2 to 5 6 Gm (normal 0 9 2 5 Gm) Losses were less than those in previously studied patients who ingested the same diet but in whom pancreatic juice was excluded completely from the intestine

Abnormal steatorrhea on the basis of fecal analysis was found in only one case of chronic pancreatitis with

(3) G t oent logy 11 791 700 N mbe 1948

out complications It was demonstrable in all patients with complications Fecal losses were roughly proportional to pancreatic damage

In four cases the studies demonstrated an otherwise unrecognized slight degree of steatorrhea and insufficiency of external secretion Thus carefully conducted studies are of value in detecting minor degrees of external insufficiency Analysis of feces for total fat gave more information in the early diagnosis of pancreatic insufficiency and of pancreatic disease than did analysis for total fecal solids or fecal nitrogen Abnormal azotorrhea does not always accompany abnormal steatorrhea and is not necessarily a part of the picture of insufficiency of external pancreatic excretion In patients with sequelae loss of calories in the stool as fat and protein reached 536 calories a day which was about six times the average loss for normal persons or for patients without sequelae

The authors conclude that occasionally in the absence of other diagnostic features intake excretion studies will provide data diagnostic of chronic pancreatitis

Chronic Relapsing Pancreatitis Analysis of 27 Cases Associated with Disease of Biliary Tract is presented by Earl E Gambill Mandred W Comfort and Archie H Baggenstoss[4] (Mayo Clinic) This condition with or without associated biliary tract disease affects males more often than females begins at any age and exhibits no predilection for the very obese In 19 of the 27 patients pain was the first symptom mentioned It is the most typical and arresting manifestation of the disease In five patients it had been present for over 10 years Character of the pain was variable It recurred as infrequently as once every four years and as often as once daily In 23 patients it was severe The possibility of pancreatitis was suggested by extension of the epigastric pain to the left upper abdominal quadrant left anterior chest left shoulder and left side of the back Seizures often lasted for days rather than hours as is character

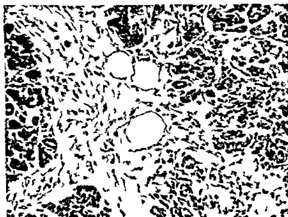
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Fig 133 (top) — R du l g on of n o a w th g t on nd ly pse docy t f rmat n n p H m t yl n nd ed d f om × 110
Fig 134 (bottom) — Ea ly p l cy t f m t n H m t yl n a d n d ce3 f m × 170
(Cou tesy f C mt ll F E t l G t nt logy 11 133 J ly 1948)

istic of biliary colic There were all manner of associated intestinal symptoms Half the patients seen during an acute attack had fever Jaundice was present in almost half the patients and about the same number had tender ness in the upper abdomen Liver was ...

patients and occasionally vague epigastric masses were felt Twenty three patients for whom data were available showed an average weight loss of 28 9 lb Diabetes was apparent in three patients and was revealed in another by a glucose tolerance test Serum amylase and lipase levels were never elevated between acute attacks but were occasionally elevated during attacks The value of doing both tests is indicated by the fact that the two



Fg 13 —At phy d d so g f ci p w th te t t l fib H m t yl d eo d d f om × 170 (C t y f G mb ll E E et l G t oe t l gy 11 1 33 J ly 1948)

enzymes were not always simultaneously elevated The secretory response of the pancreas to stimulation by secretin studied in five patients was diminished in all Steatorrhea was obvious in three patients and was detected by laboratory studies in six X rays of the pancreatic region of seven patients disclosed calcifications in five

Diagnoses made before referral of the patients included duodenal ulcer cholecystitis appendicitis and intestinal obstruction Diagnosis was suggested before operation at the Clinic for less than half the patients

Steatorrhea diabetes calcification and duration of

pain are thought to be the most important diagnostic clues Disease of the intestinal and urinary tracts and *heart must be excluded*

When a diseased gallbladder is found remissions of pancreatitis often follow cholecystectomy with or with *out choledochostomy Pain may be relieved by ephedrine* sulfate or papaverine hydrochloride or if necessary opiates A bland diet is given and use of alcohol is for *bidden Diabetes is controlled Steatorrhea is treated by* a high caloric high protein high carbohydrate low fat diet by administration of creatin tablets or by both *measures*

Necrosis with organization and pseudocyst formation frequently found in study of biopsy specimens of the pancreas of these patients is illustrated in Figures 133 and 134 Fibrosis and atrophy of later stages are shown in Figure 135

Chronic Recurrent Pancreatitis Clinical and Labora tory Aspects Figure 136 gives the incidence of symp toms of chronic pancreatitis found by R O Muether and William A Knight Jr [5] (St Louis Univ) in a study of 28 males and 30 females Although symptoms are not *specific persistence of abdominal pain food intolerance* and diarrhea especially when associated with severe exacerbations which subside on symptomatic treatment *and when not associated with gastrointestinal liver or* gallbladder disease should suggest chronic pancreatitis Pain is a constant feature and may be present in epigas trium back or right or left upper quadrant and some times may radiate to hips or neck It is continuous and characterized by crescendos

Glucose tolerance tests serum cholesterol level con sistency and composition of stool and gastric analysis were of *little use in diagnosis Serum diastase levels are* diagnostically elevated during exacerbations and may re main so during remissions The level may change signifi cantly *in a short period* making repetition of the test desirable at frequent intervals whether symptoms are

(5) G t o t ol gy 12 433 J e 194

severe or mild Normal serum diastase range lies be tween 80 and 150 units with absolute lower limit at 60 and absolute upper limit at 200 units In the present series 64 4 per cent had diastase levels of 150 or more units during remission and many had levels well above 300 units without acute symptoms

[Elman s research in acute pancreatitis has done much to stimulate our interest in and familiarize us with its symptom signs and treatment By the same token the inve tigations of

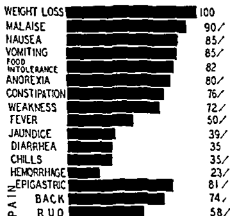


Fig 136—A ly f 58 se f h p t (Cou y f M th R O 1 k ght W A J G t oe t 1 gy 12 4 33 J y 1949)

Comfort and his associates (1946) in primary cl ron c relapsi g pancreatiti have had a similar effect with respect to the chronic form in both its latent and acute phases It is not clear from this article how many of the 58 patients had associated disease of the gallbladder Its presence would have direct bearing on symptoma tology and d agnosis If there was no such association the series is form dable and not only be peaks an enviable famil arity with the disease in its various manifestat ons but suggests an inci len e far greater than is generally supposed —Ed]

Pancreatic Calcification Study of Clinical and Roentgenologic Data on 39 Cases In the absence of surgical or postmortem examination of the pancreas evidence of pancreatic calcification is primarily a matter of roentgen visualization since there are no symptoms or signs by which calcification can be diagnosed Earl E Gambill

and David G Pugh[6] studied data on 39 patients who on roentgen examination at Mayo Clinic between 1939 and 1943 were found to have pancreatic calcification In 22 calcareous deposits were associated with relapsing pancreatitis Diagnosis of relapsing pancreatitis was made in the presence of recurrent severe usually prolonged attacks of pain in the upper abdomen provided other causes for such attacks had been excluded and there was evidence of one or more of the following (1) otherwise unexplained steatorrhea (2) pancreatic calcification on x ray surgical exploration or autopsy (3) supernormal concentration of amylase or lipase in blood serum (4) enlarged hard nodular edematous pancreas observed at surgery and (5) leukocytic infiltration interstitial fibrosis residual necrosis atrophy calcification pseudocysts and abscess formation in pancreatic tissue obtained for biopsy or at autopsy Four other patients had probable but not proved pancreatitis and eight have a history compatible with but not typical of pancreatitis Five patients had no history suggestive of pancreatitis

In patients with a history of pancreatitis time interval between occurrence of the first painful seizure and discovery of calcification varied greatly In one fifth of such patients calcification became evident within a year after onset of pain but in another fifth calcification was not discovered until after 11 22 years

Complications associated with pancreatic calcification were diabetes mellitus steatorrhea gastrointestinal hemorrhage morphinism pancreatic pseudocyst pancreatic abscess and peripheral neuritis Diabetes or steatorrhea or both occurred only in cases of calcification with a history of pancreatitis There was a hi h degree of positive correlation between extent of calcification in the pancreas and incidence of diabetes and steatorrhea Thus only 4 of 25 patients with calcification limited to the head of the pancreas had diabetes or steatorrhea whereas one of these conditions was found in 9 of 11

(6) A b I t. Med 81 301 315 M ch 1948

patients with calcification involving the entire pancreas

[Observations and conclusions of convincing nature The matter of gastroenteric hemorrhage and its possible mechanism intrigues on In the series reported by Muether and Knight (this YEAR BOOK p 7/0) the incidence was ?3 per cent and in this series 8 per cent Therefore it is logical to consider chronic pancreatitis a possible cause of bleeding of obscure origin Pancreatic carcinoma may also give rise to gross hemorrhage usually in the form of melena —Ed]

Diagnosis of Carcinoma of Pancreas Arrigo Raia[7] (Univ of Sao Paulo) reviews 10 cases observed during 1936-46 When *first seen* eight patients were *in such an* advanced stage that partial pancreatoduodenectomy was not feasible The three main reasons for the delay in diagnosis are that (1) the disease progresses insidiously and causes symptoms only in an advanced stage (2) there are no characteristic symptoms and signs of pan creatic carcinoma therefore the physician does not think of this possibility (3) physicians and surgeons still think that the chief symptom of pancreatic carcinoma is painless icterus For the first of these causes there is no practical solution but the other two can be eliminated by knowledge of the symptoms and signs of the disease

Many patients do not have icterus In a subject aged about 50 with weight loss anorexia and usually epigas tric pain roentgen examination for a gastrointestinal lesion should be made if none is found the possibility of pancreatic carcinoma should be considered and the patient examined by exploratory laparotomy

Patients who present icterus with or without pain should be suspected of having a serious disorder of the biliary passages or pancreas If they are in the cancer age a careful history should be taken and appropriate laboratory examinations made to find out whether they have pancreatic carcinoma If a definitive diagnosis is not established abdominal exploration is indicated

A special group of patients presents anorexia weight loss nausea vomiting and diarrhea before the appear ance of icterus This picture frequently deceives the phy sician and he makes the appropriate laboratory exam

(7) R d S P 1 13 63 286 J F b 1948

and David G Pugh[6] studied data on 39 patients who on roentgen examination at Mayo Clinic between 1939 and 1943 were found to have pancreatic calcification In 22 calcareous deposits were associated with relapsing pancreatitis Diagnosis of relapsing pancreatitis was made in the presence of recurrent severe usually prolonged attacks of pain in the upper abdomen provided other causes for such attacks had been excluded and there was evidence of one or more of the following (1) otherwise unexplained steatorrhea (2) pancreatic calcification on x ray surgical exploration or autopsy (3) supernormal concentration of amylase or lipase in blood serum (4) enlarged hard nodular edematous pancreas observed at surgery and (5) leukocytic infiltration interstitial fibrosis residual necrosis atrophy calcification pseudocysts and abscess formation in pancreatic tissue obtained for biopsy or at autopsy Four other patients had probable but not proved pancreatitis and eight gave a history compatible with but not typical of pancreatitis Five patients had no history suggestive of pancreatitis

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Complications associated with pancreatic calcification were diabetes mellitus steatorrhea gastrointestinal hemorrhage morphinism pancreatic pseudocyst pancreatic abscess and peripheral neuritis Diabetes or steatorrhea or both occurred only in cases of calcification with a history of pancreatitis There was a high degree of positive correlation between extent of calcification in the pancreas and incidence of diabetes and steatorrhea Thus only 4 of 23 patients with calcification limited to the head of the pancreas had diabetes or steatorrhea whereas one of these conditions was found in 9 of 11

(6) A h I t Med. 81 301 315 M h 1948

of the patients A diabetic type of dextrose tolerance curve was found in 18 of 21 patients tested and suggests that this procedure may be of greater value diagnostically than has previously been recognized

Despite lack of a radiopaque dye which can be selectively absorbed by the pancreas evidence suggestive of pancreatic neoplasm was found in 35 of 72 patients examined roentgenographically Commonest signs were irregularity of duodenal contour distortion and displacement of the stomach deformities of duodenal bulb and expansion of the duodenal loop

Although there are no pathognomonic criteria for pancreatic neoplasm and the clinical picture is somewhat variable the essential features are so definite and the procedures mentioned so helpful that diagnosis should be made earlier and more accurately than it is at present

[Recent contributions including this one have appropriately stressed the predominance of pain in the symptomatology of pancreatic carcinoma It becomes more severe as the disease progresses the u ual opiates become increasingly ineffectual and the constant suffering leads to rapid general deterioration The poor physical condition does not always permit of those surgical procedures whi h are successful to variable degree in the relief of pain of chronic relapsing pancreatitis A number of years ago Case showed that relief may follow deep roentgen therapy in certain instances and I can confirm that fact My last patient with inoperable pancreatic carcinoma experienced relief for over four months after all other measures failed and fortunately died before the pain recurred Lundy has injected a solution con isting of 0 75 per cent of ammonium sulfate and benzol alcohol (dolamin®) into the post planchnic trunk and obta ned relief for variable periods —Ed]

INTESTINAL TRACT

Hormonal and Vitamin Factors in Intestinal Absorption Theodore L Althausen[9] (Univ of California) found that in rats removal of adrenals hypophysis ovaries or thyroid glands is followed by decrease in intestinal absorption of glucose Adrenal cortex anterior pituitary and ovarian hormones affect intestinal absorption indirectly Thyroid hormone when administered to

(9) G t ent l gy 1 467 480 M h 1949

mation and arrives at the correct diagnosis too late

Finally there are patients who show the initial symptoms of anorexia weight loss and pain in a mild form and come to the physician with palpable tumor the diagnosis is made too late and radical treatment is then hopeless

[There is nothing original in these observations but one cannot stress too frequently the necessity of excluding pancreatic carcinoma in the nonicteric group especially in the absence of objective evidence of gastric carcinoma —Ed]

Carcinoma of Pancreas Diagnostic Criteria In the hope of furthering earlier recognition of carcinoma of the pancreas Grayson F Dashiell and Walter Lincoln Palmer[8] (Univ of Chicago) reviewed 90 cases in all of which diagnosis was confirmed at operation or autopsy

Predominant complaint was pain followed in frequency by jaundice weight loss anorexia constipation nausea and vomiting Pain was an extremely important and early symptom and was present in 83 per cent of the cases Although variable in character it was typically dull and persistent and located high in the abdomen but occasionally it was referred to the lower part of the abdomen It was primary in the back in 14 patients and radiated to the back in 22

Jaundice was present in 60 patients being painless in only 15 The gallbladder was palpated preoperatively in 58 per cent of the jaundiced patients

An epigastric mass was noted in about one third of the patients Progressive and rapid weight loss was prominent in 80 per cent Persistent anorexia was cited as a symptom by only 36 patients but when present it was among the earliest symptoms and therefore by itself may be significant Diarrhea though present in only 18 patients was persistent and accompanied by steady and continuous pain rather than typical cramplike intermittent pain Unexplained persistent diarrhea with abdominal pain and weight loss should therefore suggest the possibility of pancreatic disease

Glycosuria usually transient occurred in 27 1 per cent

(8) A h I t M d 81 173 183 F b r y 1948

The clinical concept of pathologically accelerated intestinal absorption with resultant signs and symptoms is advanced In patients with hyperthyroidism or Paget s disease glycosuria postprandial hyperglycemia and high oral *glucose tolerance curves are often thought to indicate* diabetes mellitus but are actually due to accelerated intestinal absorption of sugars and starches The logical diet for such a patient is one high in calories and starches Insulin should be withheld unless fasting blood sugar level is elevated High oral galactose tolerance curves are of diagnostic value in these patients except in the presence of hepatic insufficiency Patients with myxedema and Addison s disease have low oral galactose tolerance tests showing reduced intestinal absorption of carbohydrate rather than increased utilization Administration of thyroid to persons with myxedema increases intestinal absorption of glucose

In a single case of typical pellagra intestinal absorption of galactose was markedly reduced but was greatly elevated by treatment with nicotinic acid and brewers yeast

Study of Absorption of Fat and Carotene from Gastro intestinal Tract. The lipolytic hypothesis of fat absorption advocated by Verzar and McDougall in 1936 maintains that ingested fat is emulsified to soap with complete hydrolysis to fatty acid and glycerol in the small intestine intestinal mucosal cells are in a solid pavement epithelial structure fatty acids pass through the membrane as soluble complexes with bile salts while glycerides do *not pass all fatty acid is resynthesized to tri* glyceride in intestinal cells during which phosphorylation under adrenal control is essential paraffins are not absorbed and particles of fat pass into the blood stream via the lacteal lymphatic system

Frazer in 1938 suggested the partition hypothesis of fat which maintains that emulsification occurs through a triple complex of fatty acid bile salt/ lower glyceride only partial hydrolysis to fatty acids and di and mono glycerides and later glycerol is possible outer mucosal

normal rats in doses sufficient to increase basal metabolic rate by 50 per cent conspicuously increases intestinal absorption of glucose by stimulating the chemical mechanism responsible Preferential absorption of glucose is accomplished through obligate phosphorylation or conversion of each molecule of glucose to a hexose phosphate as soon as it enters a mucosal cell To complete absorption hydrolysis of hexosephosphate with liberation of a molecule of glucose must occur at the distal mucosal cell barrier before glucose can reach the circulation In dogs administration of thyroxin increased rate of glucose absorption in renal tubules but renal diodrast* excretion which does not involve obligate phosphorylation was also increased This finding and inhibition of tubular transfer of diodrast* and glucose by phlorizin permits the assumption that thyroid hormone brings about preferential absorption mainly by acting as a transmitter of oxidative energy rather than by obligate phosphorylation

Several vitamin B complex factors enter prominently into formation of enzymes which play an essential part in oxidative phosphorylation Dietary deficiency of vitamin B complex leads to pronounced decrease in preferential intestinal absorption of glucose but not in absorption of substances which takes place by simple diffusion In rats recovering from vitamin B deficiency glucose was absorbed at a greatly increased rate providing evidence of the specific role of vitamin B factors in preferential and intestinal absorption Studies in the Warburg apparatus showed that oxygen consumption of intestinal tissue slices from vitamin B deficient rats was reduced proportionately to decrease in intestinal absorption of glucose in these rats In rats recovering on a vitamin B supplement a significant increase in local oxygen consumption corresponded to the rise in intestinal absorption of glucose These facts suggest that thyroid hormone probably controls preferential and intestinal absorption through activation of oxidative enzyme systems in which B vitamins are an essentia

but the amount in the body was much less in group 3 This may have been the same distribution in group 1 and 2 when the amount of carotene was 6 mg instead of 20 mg The location of the carotene in the oil fed rats would suggest that the carotene did go along with the oil The location of the carotene in the liver is not an indication that it reached it via the portal vein —E I I

Alterations in Colonic Function in Man under Stress Experimental Production of Sigmoid Spasm in Healthy Persons Utilizing either direct proctoscopic observation or balloon kymograph technic Thomas P Almy Fred Kern Jr and Maurice Tulin (Cornell Univ) studied the functional state of the sigmoid in 45 experiments on 39 subjects who had no clinical colon disorder Stimuli used included immersion of the hand in ice water induced hypoglycemia discussion of stress producing life situations and evocation of baseless fear by special conditioning None of the stimuli solely or directly affected the colon and all were unpleasant Development of colonic changes was not related to stimulus intensity

In about half the subjects the stimuli caused increased sigmoid contractility which was associated with emotional tension and bodily reactions designed to protect the individual under stress In only two experiments did this general reaction to stress appear without significant changes in colonic function Colonic changes are part of a normal general pattern of adaptation to environmental changes regarded as threatening security

Bodily reactions correlated with colonic changes including sweating skin pallor muscle tension in neck and chest sighing and hyperventilation elevation of systolic and diastolic blood pressure conjunctival injection and reduction in gastric motility Colonic changes followed insulin administration when the lowest point of blood sugar curve had been reached and during its return to normal This coincidence suggests that sigmoid spasm is allied to general homeostatic mechanisms by which organisms adapt to an unfavorable environment

In these experiments sigmoid spasm was strikingly correlated with distinct emotional conflict Results indi

( ) G t t l gy 1 4 5 436 M h 1949

layers present a cannicular structure and fatty acids pass through the membrane either as soluble compounds or complexes while glycerides pass as negatively charged particles in a finely dispersed emulsion the adrenal cortex controls normal electrolyte balance which is closely *related to absorption of charged particles* resynthesis is not essential in the absorptive mechanism and the fatty acid fraction passes to the liver mainly via the portal system whereas glycerides pass via the lacteal lymphatic system to the blood stream and thence to the fat depots

David W Molander[1] (Univ of Minnesota) studied fat absorption in rats and the efficiency of mineral oil corn oil and fatty acids of corn oil as carriers of carotene About 65 per cent of mineral oil emulsion with particle size of 0 5 μ or less was absorbed from the alimentary tract of rats and about 66 per cent of carotene contained was absorbed Carotene absorption was similar when corn oil was used as the carrier Mixed fatty acids of corn oil were not efficient carriers of carotene across the gastrointestinal wall Most of the corn oil was absorbed from the gastrointestinal tract without hydrolysis to fatty acids but in the form of small droplets Mineral or corn oils gave systemic distribution but fatty acids of corn oil carried most absorbed carotene to the liver

[The physiologic processes concerned with the absorption of fat from the gastrointestinal tract are not clarified The authors outline the two predominant hypotheses with reference to such mechanism I requested Dr J L Bollman of the Department of Experimental Medicine Mayo Clinic to review this investigation and to comment This article leaves a lot to be desired to substantiate the conclusions drawn Table 2 of the article should also contain a control group in which the carotene was fed without being dissolved in oil The carotene was completely dissolved in the mineral oil and in the corn oil but *may* have been in the form of granules when mixed with the fatty acid The failure of absorption may have been due to the size of the carotene particles and may have nothing to do with the fatty acids present Fecal fatty acid data should have been included to show that the fatty acids were absorbed as *our rats frequently have mild diarrhea when fatty acids* are fed (*Tables* 8 9 and 10 of the article)

Group 3 rats had only a third the amount of carotene of groups 1 and 2 The amount found in the liver was similar in all groups

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(1) Y l J B l & M d 1 201 10 J y 19

600 units/cc when applied on cotton pledgets to bowel mucosa for 24 hours caused small sharply circumscribed areas of inflammation and edema Boiled tears and saline produced no lesion suggesting that lysozyme may be responsible for damaging colonic mucosa or by removing the protective mucus coating for exposing the mucosa to injury from trauma or infection That lysozyme is not the result of bowel ulceration is established by finding it in high concentration in stools of patients who have no intestinal ulcerations

[Lysozyme a mucolytic enzyme is present in stomach and bowel in higher concentration in the former Its probable role in the production of mucosal ulceration in these organs has been the subject of considerable investigation in recent years After a critical review of the literature Bargen concluded that lysozyme as a causative factor remains to be proved —Ed]

Involvement of Ileum in Chronic Ulcerative Colitis Fred J McCready J Arnold Bargen Malcolm B Dockerty and John M Waugh[4] (Mayo Found) studied 23 selected autopsy specimens of bowel and 6 surgically removed specimens of ileum from patients with chronic ulcerative colitis of the diffuse thromboulcerative type with ileal involvement In 103 cases reviewed incidence of ileal involvement was 28 per cent In the literature incidence varies from 1 3 to 39 per cent

In 22 specimens the terminal ileum was completely and diffusely involved by ulcerative changes (Fig 137) similar to those found in the corresponding colon In the other seven separate ulcers appeared intermittently in the ileum the intervening portions remaining essentially normal In all specimens the inflammatory reactions were much milder and less advanced than those seen in the diseased colons In 17 specimens with diffuse involvement of the terminal ileum average length of ileum affected was 20 cm the shortest portion being 4 cm and the longest 45 cm Of the specimens with intermittent ulcerations three were involved over several feet of the lower and upper portions of the ileum and the other four showed simultaneous involvement of both ileum and

[4] New England J Med 240 119 1 7 J 27 1949

cated that patients may respond with increased colon contractility to environmental stimuli which they regard as a threat to their security Under these circumstances the most direct and potent therapeutic device available to physicians is strong reassurance based on thorough clinical study

Studies of Human Colon Variations in Concentration of Lysozyme with Life Situation and Emotional State From studies of lysozyme concentration in stool specimens William J Grace Paul H Seton Stewart Wolf and Harold G Wolff[3] (Cornell Univ) found that in normal subjects colonic lysozyme concentrations rise in response to situational threats producing anxiety and apprehension and during periods of anger hostility and resentment The increase was not great or long sustained and was probably of little importance to the subject's welfare

In 12 patients with ulcerative colitis in remission who were enjoying relative relaxation and security stool lysozyme concentrations (0 7 1 6 units/Gm) approximated normal In four patients with mild symptoms stool concentrations varied from 13 o 25 units/Gm and in three with moderately severe ulcerative colitis symptoms concentrations varied from 40 to 100 units Day to day observations in ulcerative colitis patients showed low lysozyme concentrations during remissions coinciding with periods of relative self assurance and security During exacerbations usually marked by situations of unexpressed anger hostility and resentment there occurred sharp rises in stool lysozyme and marked elevation usually presaged a period of bloody diarrhea

Mild mucous colitis in six patients having either diarrhea or constipation was associated with low lysozyme concentration which became elevated in association with distressful life situations Lysozyme concentration was persistently low in a subject with ulcerative colon carcinoma

Human tears containing lysozyme in concentration of

(3) Am J M Sc 217 41 251 M h 1949

It is important to know whether there is ileal involvement if surgery is deemed necessary A poor operative result may follow ileostomy performed through the site of ulcerative inflammatory changes Ileal involvement is probably one of the factors that retards healing in the colon in chronic ulcerative colitis

Plumbism Simulating Acute Appendicitis Eugene L Coodley[5] (Veterans Admin Center Los Angeles) states that plumbism in both acute and chronic forms frequently simulates diverse medical and surgical disease

Man 38 was hospitalized because of generalized abdominal pain of eight hours duration and two episodes of vomiting Shortly before entry pain became localized in the right lower quadrant For the preceding 18 months similar attacks had recurred ever 3-4 months and lasted 1 3 days For the preceding three years he had worked in a lead factory assembling lead plates in batteries

There was a thin black line at the junction of gingivae and teeth There was moderate tenderness and muscle spasm in the right lower quadrant with no rigidity or masses Results of neurologic and rectal examinations were essentially normal The white cell count was 14 500 and the red cell count 4 900 000 with 0 2 per cent basophilic stippling

Appendectomy was performed and the appendix was not inflamed Blood lead content was 100 μg/100 cc (normal is 10 50 μg) and 24 hour urine porphyrin content was abnormally elevated X rays showed the alimentary canal normal Basophilic stippling did not increase on repeated test Because of a history of exposure to lead recurrent episodes of abdominal colic elevated blood lead positive reaction to a porphyrin test and a lead line along the gums lead intoxication was diagnosed

Knowledge of industries in which lead intoxication occurs is essential All forms of lead are dangerous internally especially basic lead carbonates and suboxides Lead has poisoned workers in painting and paint manufacturing pottery and tile glazing enameling of sanitary ware welding of galvanized iron lead smelting printing and industries in which tetraethyl lead fumes are prevalent Certain shampoos skin ointments face powders and paints for children s toys may cause lead poisoning

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(5) A W t M d & S g 3 43 46 F b y 1949

jejunum Microscopically ulceration included the muscularis mucosa in 20 specimens and extended through the submucosa in 4 and through the muscular layers and serosa with perforation in 5 Depth of the ulcers was independent of gross distribution and character Acute inflammatory change was noted only around perforated ileal ulcers Barium enema studies in 19 cases revealed ileal involvement in 10

Ileal involvement is not necessarily a terminal event in

F g 137 —D ff th mb l e t e l t q ffe t g e m th t th gh l oc l l t l t m l leum N t d ff ly ulce t d a d de d d m l f f l m d b f y pp c bl th k n g f all (Co rt y f M C e dy F J et l N w E gla d J M d 240 119 127 J n 7 1949)

chronic ulcerative colitis since in nine cases the ileum was involved at the time of surgery or x ray examination relatively early in the course In the autopsy cases the course in 8 had been rather acute and fulminating duration from onset of symptoms to death being a year or less in the other 15 the course was chronic Perforation occurred once in acute and four times in chronic cases Since perforation of the ileal ulcers results in generalized peritonitis and death it is one of the most dangerous complications of ileal involvement in chronic ulcerative colitis In four of the present cases perforation occurred after ileostomy

cium diet with 6 8 Gm ammonium chloride daily may liberate lead from bones into blood for excretion Sodium citrate 2-4 Gm given orally three times daily to adults may form a soluble lead citrate complex which can be excreted readily Other investigators have recommended a high calcium diet with viosterol as an attempt to increase deposition in bones without increasing excretion

Neurologic Lesions Simulating Intra abdominal Disease Painful impulses from stomach pancreas liver and biliary tracts enter the cord in the seventh to ninth thoracic segments and are experienced in the epigastric region Gallbladder pain is usually localized in distribution to the ninth thoracic nerve either anteriorly beneath the right costal margin or posteriorly at the angle of the scapula From the small intestine painful impulses reach the cord through ninth to eleventh thoracic posterior nerve roots Impulses from the aforementioned organs travel in splanchnic sympathetic pathways before entering the cord The colon is mainly supplied by afferent fibers through its mesenteries from the lower thoracic and upper lumbar segmental nerves without involvement of sympathetic or parasympathetic pathways The rectum receives afferent fibers through the parasympathetic rami from the second to fourth sacral Painful impulses from kidneys ureters and fundus uteri reach the cord via the tenth thoracic to first lumbar posterior spinal nerve roots From fallopian tubes and ovaries they reach the cord at the tenth thoracic level

After entering the spinal cord from posterior nerve roots painful impulses are transferred to a second neuron whose cell body is in the posterior horn of gray matter From here they are carried in anterior commissure to the opposite side of the cord and ascend in the lateral spinothalamic tract to the brain

According to A T Bunts[6] (Cleveland Clinic) lesions which involve thoracolumbar spinal nerve roots posterior nerve root ganglions or peripheral sensory nerves may give rise to pain simulating intra abdominal visceral disease When there is no apparent surgical emergency

(6) S Cl N th Am 8 1185 119 O t b 1948

Lead compounds are protoplasmic poisons with an affinity for nerve tissue bones and viscera Nervous manifestations are frequently diverse obscure and include peripheral palsy lead encephalopathy with convulsions coma mental confusion and severe headaches Spinal fluid usually shows moderately increased pressure positive Queckenstedt sign increase in lymphocytes slight increase in globulin and sugar and normal chloride Lead and calcium deposition and resorption from bones are generally parallel but lead localizes in flat bones ends of long bones and teeth It is usually stored in trabeculae and in children near epiphyses showing a dense line in the x ray In adults there are no characteristic x ray findings in bone Anemia may result from formation of insoluble lead phosphate which together with acid liberated makes cell walls more brittle causing rapid hemolysis

Presence of more than 1 000 cells with basophilic stippling/7 000 000 red cells is of diagnostic importance Although elevated blood or urine lead levels establish diagnosis of plumbism normal persons show a small amount of both Detection of increased urine porphyrins is useful in diagnosis Urine is acidified porphyrins extracted in an ether layer and ether extract exposed to Wood s ultraviolet filter lamp Increased porphyrins produce a red fluorescence Porphyrins may be elevated in porphyria and in poisoning by barbitals sulfonmethane tetronal sulfonethylmethane and quinine A neglected test is one in which 1 drop of 25 per cent sodium or ammonium sulfide solution is put on the skin and the area scarified if the test is positive a black discoloration appears in 8-24 hours

TREATMENT—Most treatment is aimed at increasing lead excretion Magnesium sulfate given weekly to precipitate lead sulfate in the colon and excrete it in insoluble unabsorbable form has been advocated In the acute episode use of calcium gluconate intravenously and calcium lactate orally may mobilize blood lead and deposit it in bones After subsidence lead may be liberated slowly into blood and excreted through urine and feces for a prolonged period without thera low cal

ished or absent tendon reflexes and ataxia and diagnosis Atropine may give relief from contractions of the stomach Morphine should be avoided but chloral hydrate and bromides administered per rectum may be effective Barbiturates given intravenously and x ray therapy to the dorsolumbar spine are sometimes helpful Cordotomy and posterior rhizotomy are not uniformly successful in relief of tabetic crises

With almost 70 per cent of spinal cord tumors the initial symptom is pain in many instances simulating pain of abdominal viscera Signs of spinal cord compression may not appear until later as the neoplasm expands Increased pain on coughing sneezing or straining at defecation is characteristic the pain often seems worse at night and there may be localized pain and tenderness in the spine over a tumor site Study of cerebrospinal fluid dynamics total protein content and x ray examination of the spine including myelography is often helpful in localizing a spinal cord tumor Benign tumors should be removed surgically and malignant tumors treated by both surgery and x ray therapy

Tuberculous or syphilitic osteitis of the vertebra Paget s disease primary tumors of the vertebrae secondary carcinoma erosion of vertebrae by aneurysm or extraspinal sarcoma and vertebral fractures may cause direct irritation of a posterior nerve root with resulting pain radiating to the abdominal wall Acute meningitis or chronic pachymeningitis may give rise to nerve root pain

Pain which originates in neurologic lesions such as those described often persists after surgical exploration of the abdomen has revealed no visceral disease

[The problems associated with pain mechani m and nervous pathways g ving rise to abdominal pain are gradually b ing solved The numerous contribut ons on the subject attest tl e profession s interest in and appreciation of its importance from both a medical and a surgical standpoint Certainly the unwary or preoccupied physician can easily be tripped up by those neurologic and other extra abdominal disorders s mulating abdominal visceral d sease Bunts freely and properly sub cribes to many of the tenets of Wolf and Wolff (*Pa n* [Sp ngfield Ill Charles C Thomas Publi her

the possibility of disease of spinal nerves which supply the abdominal wall should be considered

Segmental intercostal and parietal neuralgias are terms used to describe conditions associated with pain in distribution of nerves supplying the abdominal wall Although the exact cause is obscure some form of spinal abnormality chronic postural trauma mild functional scoliosis or protruded intervertebral disk may irritate or cause inflammatory reaction in emerging nerve trunks If a patient on an examining table contracts the abdominal muscles by raising his legs or head and shoulders tenderness of a true visceral lesion is decreased or absent on abdominal palpation while tenderness of a parietal neuralgia is readily elicited Orthopedic measures elimination of foci of infection or various types of nerve block may give relief Spinal arthritis or neuritis may also produce this syndrome

Herpes zoster an acute virus infection involving posterior nerve root ganglions posterior nerve root peripheral nerve posterior horn of gray matter of the spinal cord and the corresponding skin area usually manifests itself by burning or shooting pain in the segment involved associated with hyperalgesia of skin Papulovesicular eruption of skin occurs three or four days after onset of pain and follows a zonal pattern in involved dermatomes It is usually unilateral In the early stages repeated daily subcutaneous injections of 1 cc pituitrin* or deep x ray therapy to the nerve roots and their ganglions may give relief For prolonged postherpetic neuralgia posterior rhizotomy cordotomy or frontal lobotomy should be carefully considered as methods of relief

Tabes dorsalis is often accompanied by severe paroxysmal stabbing pains of short duration which are attributable to an irritable state of degenerating sensory fibers in posterior nerve roots Gastric crisis is the commonest disturbance involving a hollow viscus and is characterized by epigastric pain associated with severe vomiting A previous history of syphilis blood serologic tests loss of vibratory sense pupillary changes dimin

symptoms of complications rather than of the usual cardinal symptoms of the condition

Laboratory observations in these cases are presented in Table 2 X ray examinations of the bones may show osteoporosis in adults and rickets and deformities in children The colon may be large and atonic and the small bowel may show obliteration of herringbone markings due to the valvulae conniventes moulage formation dilatation clumping of barium and hypomotility

TREATMENT —Diet must be fluid at first given in frequent

TABLE 2 —LABORATORY OBSERVATIONS IN 30 CASES OF SPRUE

O A S	C s s
Anemia	24
Macrocytic	18
Stool—increased fatty acid crystals	29
Serum calcium—below 9 mg /100 ml	18
Not done	5
Serum phosphorus—below 3 mg /100 ml	11
Not done	14
Ewald test—normal	11
Hypochlorhydria	12
Hyperchlorhydria	2
Not done	5
Serum proteins—below 6 Gm /100 ml	14
Not done	13
Oral glucose tolerance curve—flat	9
Normal	2
Not done	19
Prothrombin time—low	3
Gastroscopic picture—normal	2
Atrophic gastritis	1

small feedings and increased until the patient is receiving 150 Gm protein and 300 Gm carbohydrate a day Fat content is kept low and increased as tolerated Crude or refined liver extract 2 cc /day is given parenterally Folic acid is specific for the anemia of sprue and is given initially in 10-20 mg daily oral doses followed by maintenance doses of 2 5 5 mg daily Vitamin B complex 2 cc /day is given parenterally but later may be administered orally Because of negative calcium balance calcium lactate 15 gr three times a day should be given Vitamins A and D are prescribed in 1 cc daily doses of viosterol or halibut oil Vitamin K may be used if prothrombin time is low If the patient is still unable to gain because of impaired fat absorption tween 80® (polyoxyalkylene ether of sorbitan mono-oleate) may be used in doses of 1 5 Gm be

1948]) to the observations of Judovich and Baker (*Segmental Neuralgia in Painful Syndromes* [Philadelphia F A Davis Co, 1946]) as well as to those of Garnett a pioneer worker in this field —Ed]

Idiopathic Steatorrhea Report of 30 Cases In the syndrome described by Charles H Brown[7] impaired absorption of fat results from some change in the mucous membrane of the small bowel Increased fat in the stool causes diarrhea lack of absorption of intrinsic factor causes macrocytic anemia lack of absorption of calcium and vitamin D results in skeletal changes and tetany and lack of absorption of vitamins A B and K causes skin changes and lens opacities glossitis and stomatitis

TABLE 1 —SYMPTOMS IN 30 SPRUE PATIENTS AT CLEVELAND CLINIC

Symptom	Cases
Diarrhea	27
Loss of over 20 lb	21
Sore tongue	12
Flatulence	11
Edema	8
Osteoporosis (symptoms from)	6
Tetany	5
Anorexia	5
Hemorrhage	3
Pernicious anemia	1

and a hemorrhagic picture respectively There are few significant pathologic changes in the intestine Steatorrhea may be due to lack of bile or pancreatic secretions secondary to gastrectomy gastrocolic or jejunocolic fistula mesenteric lymph node disease lymphatic obstruction intestinal lipodystrophy regional enteritis protozoan or bacillary dysentary or amyloidosis of the small intestine or it may be primary as in tropical and non tropical sprue and celiac disease

Because of the multiple causative factors the clinical picture is often confusing The primary complaint may be associated with lack of any one of the essentials listed earlier Symptoms in cases which Brown studied are listed in Table 1 Patients usually complained of

(7) Cl 1 nd Cl Q t 16 52 58 J n a y 1949

laws of gravity differentiates a collection of free gas from megacolon or meteorism in which the area of vibrations is not displaced when the patient turns from one side to the other Of 20 patients with intestinal perforation from various causes all had the sign even when the examination was made during the first 30 minutes after onset of pain whereas the other signs of perforation or of pneumoperitoneum were found in a varying percentage of patients but never in all (Fig 138)

There can be no doubt of the importance which this sign will acquire in the search for a syndrome difficult to recognize in its early stages before many of the classic signs have developed A technical condition to be observed in determining the presence of vibration and consequently of gas in the abdominal cavity is to place the patient on his back with shoulders lower than the hips so that gas may leave the subphrenic space and accumulate in the epigastric or umbilical region where the vocal vibrations can be easily discovered on palpation

Mesenteric Vascular Occlusion According to James E Musgrove and Carl G Morlock[9] mesenteric vascular occlusion [though relatively rare—Ed] is one of the most catastrophic of all abdominal emergencies The patient s condition may be so poor at onset of the illness as to preclude surgery Even if operation is possible involvement may be so extensive that adequate bowel resection cannot be carried out with any hope of survival However minor degrees of mesenteric vascular occlusion can occur with little disturbance to the patient and full recovery result without surgical treatment

Males are more frequently affected than females The patient may be of any age Etiologic factors include heart disease and arteriosclerosis infections which cause thrombophlebitis such as appendicitis pelvic abscesses peritonitis or general sepsis hematogenous factors such as blood dyscrasias splenic anemia and polycythemia vera trauma to the mesenteric vessels particularly at the time of operation and mechanical factors which re

(9) P Staff M t M Cl 3 5 1 5 8 N 10 1948

f re each meal to facilitate emulsification and absorption of fat

Although usually symptoms promptly disappear and oral and glucose tolerance rapidly become normal the flat vitamin A tolerance curve persists indicating that the basic difficulty fat absorption in the small intestine is not corrected by treatment with folic acid or liver extract Because irreversible damage may occur it is important that patients be treated intensively

New Sign of Intestinal Perforation or of Pneumoperitoneum Abdominal Vibration Guglielmo Carbonelli[8]



Fig 139 A Sg f l l m) l B Abdominal d f se C El m t f h p t l l D Ral ol g lly l m nt l l g Bl k port on f c l mn l at gn p se t d g l l gn p t lly p se a l wh t po t n d se t tl ou t y f t bo (Schw z med W b sch 9 17 1 3 F l 6 1949)

(Univ of Bologna) states that when there is gas free in the abdominal cavity and the patient pronounces a word rich in dental consonants the examiner s hand applied to the abdominal wall over the area containing the gas feels vocal vibrations transmitted to this area but nowhere else The fact that the area of vibrations changes with changes in the patient s position in accordance with the

(8) S h z med W h ch 79 17 1 3 F b 26

state that use of streptomycin completely alters the out look for phthisic persons in whom diarrhea develops It was uniformly effective in relieving symptoms of tuberculous enteritis After initiation of treatment by the intramuscular route improvement occurred in 20 pa tients within one week Relief of diffuse and localized abdominal tenderness rigidity and distention came a few days *after relief of abdominal pain Eighteen patients* had diarrhea when streptomycin was started and by the end of the first week the average of six liquid stools daily had been reduced to two formed stools Occult or gross blood mucus and pus noted in eight cases disap peared as the stools became normal Temperatures re turned to normal levels Weight was rapidly regained During or after relief of intestinal symptoms the sputum of eight patients became negative more intensive study with longer follow ups will tend to increase this number

Eight patients are still under treatment and 25 have been followed 1 16 months since treatment was started or 2 weeks to 12 months since streptomycin was discon tinued Two have had a definite recurrence of symptoms One patient treated only for relief of symptoms had striking relief in the short period before death

X ray study including fluoroscopy in 17 cases re vealed abnormalities in all before treatment In six the picture returned to normal after treatment Eight showed definite improvement but some residual deformity Marked *residual abnormality was noted in two cases* and in one signs of small bowel obstruction developed Normal x ray picture can be expected provided the ab normalities are primarily those of local irritation If ulceration has been deeper more widespread and of longer duration and if lymphatic and interstitial obstruc tion has destroyed the normal architecture of the bowel wall *irreversible changes* may persist and cause further distortion due to contraction of residual cicatrix How ever this is important only if continued contraction leads to bowel obstruction

Treatment varied from case to case At present it is

sult in portal stasis such as pressure from intra abdominal tumors Occlusion of either arteries or veins may result in hemorrhagic infarction arterial occlusion is more frequent Endarteritis or arteriosclerosis may produce slow closure with intermittent symptoms

Symptoms are not definite and may be those of acute intestinal obstruction strangulation of the intestine rupture of a viscus or peritonitis Pain vomiting distention constipation diarrhea and shock may occur Rather commonly the pain commences about one hour after the evening meal

Treatment depends on the patient s general condition and severity of the lesion If feasible exploratory laparotomy should be performed When there is the slightest doubt as to viability the involved intestine should be resected If the bowel is viable conservative treatment is recommended Because of blood lo s into the bowel lumen transfusions as indicated are imperative Continuous gastrointestinal decompression should be applied In a case treated conservatively beginning 12 hours after laparotomy 50 mg heparin was given every four hours until the suction tube was removed when 200 mg dicumarol* was given daily Papaverine hydrochloride was administered in ½ gr doses every four hours for four doses Although not used in this ca e sulfonamides *or suitable antibiotics should be of definite benefit*

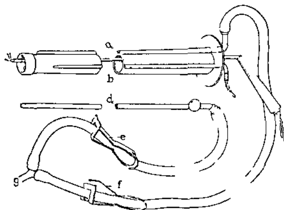
[In this instance the results of conservative treatment were successful The small bowel was considered viable at operation and was not re ected Before the abdomen was closed a Miller Abbott tube was pas ed intranasally and gradually worked down into the ileum For further details regarding postoperative management and progress the reader should consult the original article This is just another example of how modern mechanical aids and pharmacologic agents make for effective pre and postoperative treatment not po sible a decade or two ago —Ed]

Streptomycin in Treatment of Tuberculous Enteritis Report of 33 Cases On the basis of a co-operative study of 33 patients from 15 Veterans Administration hospitals Edward F Mason William W Kridelbaugh William H Crouch and Melgie Ward[1] (Wadsworth Kan)

(1) Am J M Sc. 17 8-46 J ry 1949

comitant disease One patient survived nine years another eight and the rest two years or less

Pedunculated polyps regardless of size or position can be fulgurated provided exposure of polyp and entire pedicle is adequate Small sessile lesions (less than 6-8 mm if in mobile portion of sigmoid) can be successfully fulgurated with little regard for their position Large sessile polyps may be fulgurated if located on



F g 139—F lg t g p t p w th t pp t t he f m k b t b f l ght f lg t g l t d d t t he f l q d d f l mp H t b g t p m t p t f th m k or l q d g gl t w th f (C t f B L A t l J A M A 139 0 709 M 1 194))

the posterior wall of that portion of rectum not covered by mesentery In that location bowel wall may be destroyed without danger of injury to vital structures In treating malignant lesions the bowel wall should always be destroyed and unless properly located should not be fulgurated unless operation is contraindicated for other reasons or refused The least degree of firmness or limitation of mobility in a lesion suggests malignancy Large disseminated polypoid lesions and those with adjacent mucous membrane hyperplasia respond poorly to fulguration and should be treated by radical surgery

recommended that 1 Gm be given intramuscularly in two daily doses. This dose carries a 23 per cent incidence of vertigo as compared with 94 per cent when 2 Gm daily is used. Although 19 patients completed courses of 60-120 days, there was little uniformity in the length of treatment in this series.

[The discouraging refractoriness of this form of diarrhea and its debilitating systemic effect are well known. The authors properly warn us of the neurotoxic properties of streptomycin, especially in the form of involvement of the vestibular branch of the eighth nerve, leading to vertigo, which may prove stubborn and disconcerting. Such a complication is more likely to occur when large doses are necessary over a long period, as in the treatment of tuberculosis, acute brucellosis and acute infectious endocarditis. Fortunately the hazards of streptomycin therapy have been reduced in the past two years by the development of dihydrostreptomycin, a chemical modification. This is distinctly less neurotoxic but retains the therapeutic potentialities of the parent preparation. For further particulars see H. F. ... et al, this Year Book, p. 22.—J. H.]

Polypoid Lesions of Terminal Portion of Colon with Special Relationship to Fulguration. According to Louis A. Buie, Newton D. Smith, Raymond J. Jackman and John R. Hill[2] (Mayo Clinic), fulguration is an effective method for treating polypoid rectosigmoid lesions, but great care must be used in selecting patients to be treated. For 457 patients with polyps up to 5 cm. in diameter, fulguration or fulguration and radium was considered the best treatment, and six months to over five years later only two had lesions at the original site.

Operation was inadvisable for or refused by 34 patients with sessile and 5 with pedunculated lesions. Biopsy disclosed adenoma in 1, adenocarcinoma in adenoma in 15 and adenocarcinoma in 23. Fulguration was carried out in 11 and fulguration followed by radium in 28. All were re-examined over six months later and 14 over five years later, and in 11 lesions were found at the original site.

Fulguration was administered as a palliative measure to eight patients with adenocarcinomas because the lesions were inoperable, the patient refused radical operation or operation was contraindicated because of con-

(2) J. A. M. A. 139:70-09, M... 1, 1949.

comitant disease One patient survived nine years another eight and the rest two years or less

Pedunculated polyps regardless of size or position can be fulgurated provided exposure of polyp and entire pedicle is adequate Small sessile lesions (less than 6 8 mm if in mobile portion of sigmoid) can be successfully fulgurated with little regard for their position Large sessile polyps may be fulgurated if located on

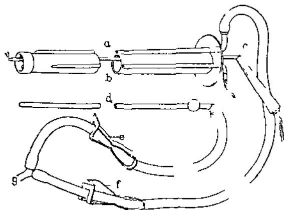


Fig 139—F lg t g p octosc p w th t pp t t l f m k b t t f l ght f lg t g l ct d d t t l f l q d d f l mp bb t b g t p m p t f th m k l q d g gl t w th f (C t y f B L A t l J A M A 139 70 709 M l 1949)

the posterior wall of that portion of rectum not covered by mesentery In that location bowel wall may be destroyed without danger of injury to vital structures In treating malignant lesions the bowel wall should always be destroyed and unless properly located should not be fulgurated unless operation is contraindicated for other reasons or refused The least degree of firmness or limitation of mobility in a lesion suggests malignancy Large disseminated polypoid lesions and those with adjacent mucous membrane hyperplasia respond poorly to fulguration and should be treated by radical surgery

[illegible]

Diverticulosis of Colon. Review of 726 Consecutive Cases. According to Franklin H. [illegible] and L. N. Collins,* the exact cause of diverticula of the colon is unknown. They occur most frequently in the sigmoid colon and rarely in the rectum. In the present series 75 per cent of the patients were age 50 or over. About 65 per cent were overweight.

In general, symptoms and physical findings were similar to those seen in a series of cases of irritable colon. Abdominal distress or pain, gas, constipation and to a lesser extent nausea and vomiting were common complaints in both conditions. The similarity of symptoms and response to treatment are more than coincidental. It seems logical that the diverticula are the result of the irritable colon or become larger as the result of altered function of the irritable large bowel.

In this series 121 patients had organic gastrointestinal disease. Gallbladder disease and duodenal ulcer were the conditions most commonly encountered. Cancer of the gastrointestinal tract was associated with diverticula of the colon in 24 cases.

Diagnosis of diverticulosis is made by exclusion of other possibilities and can be substantiated only by x-ray examination.

(3) Cleveland Cl. Q. [illegible]

Treatment is based on prevention of future complications and elimination of underlying causes Undue emotional upsets and nervous or physical exhaustion should be avoided as far as possible Weight reduction is desirable for the obese person Small weekly or biweekly doses of barium sulfate may be given in the hope that this inert substance will fill the diverticula and prevent further irritation The diet should be of a low residue type with avoidance of seeds skin and coarse fibers Treatment of constipation includes ample sleep and rest adequate fluid intake habit time and use of one of the bland bulk producing preparations until the rectum is retrained to a habit time For unduly hard stools use of a 3 oz oil retention enema before retiring will usually result in a soft stool the next morning Initially antispasmodics or some related compounds with small doses of phenobarbital will aid in reduction of spasm of the colon and relaxation of the patient The nature of the illness should be discussed with the patient and its relative innocuousness stressed Prognosis for uncomplicated diverticulosis under proper management is excellent

[Exclusive of barium sulfate the treatment recommended is the conventional one and has usually proved quite effective The authors hoped that the barium would fill the diverticula and, because of its inertness would prevent further irritation However they caution against its administration in the presence of partial or impending obstruction —Ed]

MISCELLANEOUS

Comparative Therapeutic Effects of Dextro and Racemic Amphetamine Sulfate From a study of 105 patients S Charles Freed[4] (San Francisco) concluded that dexedrine® and benzedrine® are approximately equally effective in curbing appetite for weight reduction purposes With dexedrine® there is a lower incidence of side reactions such as nervousness nausea headache palpitation and dry mouth Constipation is equally fre

4 J S g 57 67 70 F bru ry 1949

with achlorhydria are bifidum negative Lack of gastric acid to stimulate pancreatic secretions is accompanied by inadequately digested protein products and is another factor which enhances intestinal putrefaction

To increase colon Bact bifidum population and hence increase colonic acidity and decrease putrefaction in the aged several therapeutic measures are recommended Food must not be too rich in protein but milk proteins do not putrefy as readily as those in meat To aid in sterilization of food as it leaves the stomach a little hydrochloric or citric acid should be taken at mealtime Similar results may be achieved by eating acid fruits or pickles and drinking acid drinks such as wine or sour milk products Food should contain ample amounts of dextrin or dextrin forming substances such as starch Milk sugar content of milk may be increased by adding milk sugar complements In some cases milk cultures of Bact bifidum may be required

[For supplementary reading I recommend an art cle by Johansson and Sarles (Bact Rev March 1949) entitled Some Considerations of the Biological Importan e of Intestinal Microorganisms —Ed]

Treatment of the Fat and the Lean is discussed by Clifford F Gastineau (Mayo Found) Edward H Rynearson and Alice Karslake Irmisch[6] (Mayo Clinic) Under and overweight are of great importance in health Even moderate obesity in the latter half of life increases incidence of many degenerative diseases including hypertension diabetes cancer heart disease nephritis arteriosclerosis toxemia of pregnancy cirrhosis of the liver emphysema and varicose veins A reduction program is of importance in combating such diseases Though underweight is reported to increase susceptibility to tuberculosis moderate underweight is desirable in persons past 40

Cause of obesity and leanness is disproportion between caloric intake and caloric requirements Therapy of these conditions therefore consists of correction of this disproportion by diet Psychologic factors are often of

(6) J A M A 139 86 91 Jan 8 1949

quent with both drugs There seems to be no decreased tolerance to dexedrine® following use of benzedrine®

Either drug may be used in treating obesity but choice depends to a certain extent on constitution and personality of the patient Benzedrine® seems less suited to persons with a more sensitive and responsive nature to drugs pain and intrinsic or extrinsic stimuli Those of the opposite type seem to prefer benzedrine® Hyper sensitive persons cannot tolerate too well the adrenergic action of levo amphetamine present in benzedrine® and therefore prefer dexedrine®

Senility and Intestinal Flora Re examination of Metchnikoff's Hypothesis To evaluate Metchnikoff's theory that senility and shortening of life are linked with *intestinal putrefaction* S *Orla Jensen Erik Olsen* and Torben Geill (Copenhagen) compared intestinal flora of normal persons aged 30-40 with that of persons over 70 In the older group there were 31 senile and 32 nonsenile persons sex distribution was about equal Streptococcus salivarius and putrefactive bacteria such as Clostridium welchii were most numerous in the aged and Bacterium bifidum in the younger group In the aged colon acidity was low whereas in the younger group it was high be cause of acid produced by Bact bifidum during diges tion of nonabsorbable sugars

Gastric and colon acidity are barriers to growth in the colon of Str salivarius and Cl welchii organisms responsible for intestinal putrefaction Gastric achlor hydria or hypochlorhydria were common in the older group thus permitting Str salivarius to migrate from the mouth to the colon and be identified in the feces of these persons *Small intestine contents of normal per sons* are almost free from bacteria because of gastric acidity In persons with achlorhydria small bowel con tents are heavily infected with lactic acid bacteria which convert all nonabsorbable sugars into lactic acid Be cause dextrins and milk sugar do not reach the colon Bact bifidum cease multiplication Hence mo t people

(5) J C ront 1 4 5 15 J ary 1940

peptic ulcer The operative risk in the ulcer patient is also enhanced because of a severe cough due to chronic irritation from tobacco the *bronchitides fumère* of the French The less frequent opposite of the obese patient is the psychoneurotic with anorexia nervosa and marked malnutrition Such patients usually require skilful individualized psychiatric and dietetic management and despite this the prognosis is guarded owing to the predisposition to relapses —Ed.]

importance in the genesis of obesity Imitation of elders and attitudes acquired in childhood govern eating habits of later life Certain conflicts may cause polyphagia in one person and anorexia in another and yet have no effect on the appetite of a third The term Frohlich s syndrome or adiposogenital dystrophy is often unjustifiably applied and should be restricted to obesity in sexually *immature males who are definitely older than age* of normal puberty and have real evidence of a lesion in the region of the hypophysis and hypothalamus Endocrine factors are rarely a cause of pronounced obesity or leanness Cushing s syndrome causes obesity but is extremely rare Islet cell tumor of the pancreas is frequently associated with obesity owing to the increased food intake *necessary to relieve attacks of hypoglycemia but this* condition too is rare Neither Plummer in his study of spontaneous myxedema nor Sheehan and Murdock in their study of postpartum pituitary insufficiency were able to find any increased incidence of weight abnormalities in patients with hypothyroidism or hypopituitarism Emaciation may be due to anorexia nervosa which usually *appears in nervous women under 30*

The authors rarely find it necessary to use amphetamine *derivatives such as benzedrine® or dexedrine®* as an adjuvant to reducing diets Psychotherapy has in their experience been of great importance in treatment of both under and overweight persons They have not used diuretics atropine digitalis thyroid or other endocrine preparations massage or exercise as integral parts of weight reducing programs Use of insulin is impracticable and vitamins usually fail to stimulate appetites of underweight subjects

[Among the bugbears of daily med cal practice are obesity psychoneurosis cigaret abuse and less frequently drug addiction The obese patient usually the middle aged man or woman with a gluttinous tendency of variable degree frequently attributes his or her excess weight to *anything other tha faulty eating habits* And such individuals may persist in this even though they are aware of the risk of an impending operation or the aggravation of degenerative processes The same holds true for the cigaret fiend afflicted with coronary or peripheral vascular chro

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